1.1 Head and Neck Cancer

1.1.1 Diagnostic Ultrasound in Head and Neck Oncology

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Modern ultrasound machines produce in real time high quality images of soft tissues. Ultrasonography is recommended as the first imaging technique of choice for suspected soft tissue pathology in the head and neck or staging of cervical lymph nodes in patients with suspected or proven oropharyngeal neoplasms. It is noninvasive, inexpensive and quick to perform. In contrast to computer and magnet resonance tomography contrast media are not needed for sonographic evaluation. Therefore sonography can also be used for a close noninvasive follow up.

Other imaging techniques such as computer and magnet resonance tomography may also be indicated for staging purposes and for the evaluation of extended neoplasms especially when there is bone infiltration or tumor growth deeper than 40 mm. For the sonographic evaluation of 7.5 MHz scanner are routinely used in the head and neck. The sonographic appearance of typical oncological sonographic findings in the head and neck will be presented and correlated with the clinical picture.

1.1.2 Diagnosis and Surgical Therapy of Lymphatic Drainage of Upper Aerodigestive Tract Tumors

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Regional metastases to cervical lymph nodes are most frequently disseminated from squamous cell carcinomas of the head and neck region. Thus, the most encountered such malignancies are carcinomas originating in the mucosa of the lips, oral cavity, pharynx, and larynx. The topographic pattern of tumor spread in the neck is determined by the anatomy of the cervical lymphatics and the location of the primary tumor. The diagnosis of palpable cervical lymph nodes has been to a certain extent controversial for many years and continues to be an evergreen topic. The ultrasonographic battery (B-mode, Doppler, and color-coded duplex ultrasonography) has established itself during the last two decades as an indispensable diagnostic modality in the head and neck region. With its high sensitivity (90–97%), B-mode ultrasonography clearly exceeds the detection capability of enlarged lymph nodes by palpation (69%), computerized tomography (83%), and magnetic resonance imaging (83%). As a rule, the surgical management of cervical lymphatic drainage of malignant head and neck tumors consists in their comprehensive clearance by neck dissection. On this subject one can find a multitude of partly contradictory reports and opinions in the literature, reflecting the inconsistency of the proposed surgical treatment strategies. Based on a standardized classification of cervical lymph node echelons and neck dissection procedures, the evaluation of prognostic and recurrence risk factors is an important aspect in the management of the individual patient. In a retrospective review of our squamous cell laryngeal carcinoma patient population, we attempted to evaluate by uni- and multivariate analysis the statistically independent factors affecting prognosis and risk of recurrence. Between 1984–1998 we operated 462 patients (438 males, 24 females), with a median age of 61.5 years. The tumors were 58% glottic, 30.7% supraglottic, 2.6% subglottic, and 8.7% transglottic in location. The survival was calculated according to Kaplan-Meier, the univariate analysis was performed by means of the Log-rank test, whereas for multivariate analysis we used the Cox proportional hazard model. The median follow-up period to the date of evaluation (January 1, 2000) was 6.3 years. The overall 5-year survival was 63.6% (median 9.4 years), the disease-free 5-year survival 56.1% (median 7.9 years). According to tumor location, the overall 5-year survival was 74.7% in patients with glottic carcinoma, 49.5% in those with supraglottic carcinoma, 56.3% in subglottic carcinoma, and 41.5% in transglottic carcinoma patients. The main independent prognostic factors affecting lymph node metastasis found by multivariate analysis were the pretreatment patient morbidity, the pretreatment hemoglobin content, the tumor location (supraglottic, glottic, subglottic, transglottic), and the presence of hoarseness as symptom. One-hundred-and-twenty patients (26%) developed tumor recurrence, and in this group the median disease-free period was 10.2 months (mean 1.3 years). The most important independent prognostic factor of disease-free survival found by multivariate analysis was the extent of lymph node dissemination at the time of the primary operation. Additional statistically independent factors of influence on recurrence appeared to be the pretreatment hemoglobin in serum, the pretreatment patient morbidity, the tumor grading, the patient’s age at the time of primary therapy, a history of a second malignancy, and the state of residual tumor. The determination of prognostic and recurrence risk factors of laryngeal carcinoma allows a rational and pragmatic deployment of surgical strategies and enables the early identification of patients with high risk of recurrence during follow-up.

Deep neck infections and abscesses represent a special challenge to otolaryngological diagnosis and therapy because they may develop independently of primary manifestations of lymphatics-disseminated malignancy of the upper aerodigestive tract. Neck abscesses belong invariably to the dangerous clinical entities that require rapid diagnostic and therapeutic intervention. Despite protean antibiotic treatment possibilities, deep neck infections still occur frequently and continue to carry a high rate of morbidity and mortality. One-hundred-and-two patients were examined throughout a period of five years (January 1997 through December 2001). Tonsillogenic neck abscesses and those originating in sialadenitides were not considered. The infection could be ascribed in 17 patients to abscessing lymphadenitis, and in 85 patients to deep neck infection. The median age was 37 years (youngest 1 year, eldest 89 years of age). There were 57 males and 45 females. The most frequently found pathogens were streptococci (n=25), staphylococci (n=19), and anaerobic bacteria (n=25). Particularly striking was that in seven patients the neck abscess was the presenting manifestation of the malignancy. Cat-scratch disease with suppurring lymph nodes was found in 10 cases, while abscessing lymph node tuberculosis was present in 6 patients. The adequate and wide-spectrum antibiotic therapy, surgical drainage, and airway patency preservation are the mainstay of therapy. Only in cases of superficial, uniloculated, limited abscessing lymphadenitides with a preexisting causative agent (e.g., Bartonella henselae, Mycobacterium tuberculosis) the dictum

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‘ubi plus – ibi evacua’ can be dispensed with in individual cases. The relatively high rate of 6.9% of malignancy-associated neck abscesses justifies in our view, besides surgical drainage, an unfettered indication for simultaneous panendoscopy and biopsy to rule out an underlying or different pathological entity (i.e., tumor) in the head and neck. This particularly holds true when the portal of entry is obscure (e.g., foreign body in the pharynx), or in the presence of risk factors (nicotine and alcohol abuse). Hence, the occasional diagnosis of malignancy may be clinically and histopathologically established sooner, with an early subsequent institution of therapy. Thus, in the diagnostic work-up of a neck abscess, histopathology has an equal importance to the microbiological detection of the pathogen.

1.1.3 Diagnostics, Therapeutic Procedures and Rehabilitation in Tumors of the Paranasal Sinuses

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Tumors of the paranasal sinuses often are of large extent when the patients consult an ENT-specialist for the first time. In many cases an adherence or infiltration of adjacent structures like the orbit or the intracranial space results in the first relevant symptoms. Another aspect is the fact that surgical procedures to the sinuses may result in an obvious alteration of the facial contours, touching cosmetic aspects. Thus, surgical interventions have to be well considered and to be associated with a reconstructive strategy in many patients. Diagnostic steps in patients start with a well-structured medical history focusing on symptoms resulting from potential affection of the orbit or the brain. ENT-endoscopy of the nose and biopsy of the tumor are mandatory, and CT-scans (showing bone destruction) and MRT (showing orbital or meningeal infiltration) are performed in most cases and supplemented by an ophthalmologic examination. The therapeutic strategy depends on the extent of the tumor and its exact histologic feature. In solid tumors of adult patients (sarcoma, carcinoma), a surgical resection followed by external beam radiation is the best strategy for most patients. In tumors of large extent, an interdisciplinary strategy may be necessary to reach the best therapeutic and rehabilitative results. Intraoperative computer navigation in a Skull Base Center allows to exactly localize crucial structures like the optic nerve. Additionally, by navigation an optimal reconstruction of facial contours and the orbital floor (e.g. with titanium implants) can be achieved. Soft tissue sarcoma in children demands close collaboration with an oncopediatric center from the beginning of diagnostics and is usually treated with standardized protocols. We conclude that patients with a tumor of the inner nose or the paranasal sinuses should be treated in a specialized center from the beginning of diagnostics. Safe and sufficient removal of the tumor as well as an optimal functional and cosmetic reconstruction require a high technical standard.

1.1.4 Resection of Malignomas in Oral Cavity, Pharynx and Larynx by Laser Surgery Controlled by Endoscopy/ Microscopy

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There are several procedures for the surgical treatment of tumors of the oral cavity, pharynx and larynx that comply with the requirements of safe removal of the tumor in sano as well as extensive protection of functional decisive structures. One of the prerequisites of the development of partial resection was, apart from the imaging diagnostics, the information on the histological tumor extension (e.g. direction of the growth, anatomical barriers) and the functional processes, as well as the improvement of the endoscopic examination methods. The main objective of tumor therapy, apart from making a diagnosis as early as possible, is the complete tumor removal with minimal functional loss. This is often a problem for the treating surgeon, as the oncological success is achieved at the expense of function in most cases, especially in large carcinomas.

In the case of small, isolated neoplasias limited to the surface, a transoral approach should be preferred instead of conventional surgery from outside, as this procedure obtains the same results but is much less of a strain for the patient.

Laser surgery of malignant diseases of the upper aerodigestive passage, controlled by endoscopy and microscopy, is gaining in importance. The possibility of transoral interventions has been enlarged considerably. Meanwhile CO₂-laser is widely accepted for clinical use in enoral tumor surgery. The strategy of surgery differs from the normal procedure. The extension and infiltration of the tumor is asserted endoscopically and with the help of radiological scanning; and a biopsy is performed. Generally, a transoral resection is performed according to the tumor extension identified during surgery. The use of the microscope enhances the oncological safety, as early carcinoma stages can be detected more easily. Immediate intraoperative pathological examination can confirm a resection in sano, if needed. A second resection might have to be performed after receiving the final histology. The advantages, risks, and limitations of tumor resection by laser surgery will be presented on the basis of several case studies.

1.1.5 Management of Orbital Tumors

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Typical clinical signs of orbital tumors are exophthalmus, abnormal eyelid position, motility disturbance and compression of the optic nerve. Patients may complain about sensation of retrobulbar pressure and pain, double vision or decreased visual acuity. If an orbital tumor is suspected, a MRT should be obtained, usually with fat suppressed T1-images. Gadolinium may rule out inflammatory processes. An additional CT may show the integrity of the surrounding orbital walls. If the diagnosis is still uncertain after neuroradiologic examination, a biopsy is indicated. The spectrum of therapy comprises surgical removal, radiation and chemotherapy. The choice for one or more of these procedures depends on the kind of tumor.

The surgical approach depends on its location: Tumors within the muscle cone can be removed transconjunctivally, tumors outside the muscle cone should be removed transcutaneously, possibly under temporary removal of the lateral orbita wall. If the tumor is located in the medial part of the orbit, surgery should be performed together with an ENT-specialist removing the ethmoidal cells in order to facilitate the approach.
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Prognosis of Squamous Cell Carcinoma in Atopic Dermatitis

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Universitäts-Augenklinik Freiburg

Introduction: Squamous cell carcinoma has a rather good prognosis in immunocompetent patients. However, the clinical course is worse in atopic dermatitis. This is a new finding which has to be considered in our treatment strategy. Patients: Six patients with severe atopic dermatitis were treated for squamous cell carcinoma of the lids (n = 3) or for conjunctival squamous cell carcinoma extending onto the tarsal conjunctiva (age 28–72 years, m = 46 years). Clinical course: 2 patients primarily presented with regional lymph node involvement proven by sonography or biopsy. Further 3 patients developed metastasis 5 to 10 months after tumor excision and 2 of these patients up to 10 years later had a second squamous cell carcinoma on the fellow eye. In 4 patients a neck-dissection and/or a radical parotidectomy were performed. 3 patients had radiotherapy (60 Gy). 2 of the 6 patients died within 11 and 18 months. Results: Due to the rapid growth the differentiation from keratoacanthoma was difficult. Furthermore, the young age of the patients, the bilateral involvement, the rather high incidence of regional lymph node metastasis, and the aggressive tumor growth were unusual. In 3 patients the tumor was associated with a human papilloma virus infection. Conclusion: Patients with severe atopic dermatitis are in danger to develop multiple rapidly growing squamous cell carcinoma of the lids which may develop early metastasis. Careful sonographic examination for regional lymphadenopathy has to be performed before pretreatment biopsy. Otherwise postoperative inflammatory reaction may mask regional lymph node metastasis. The difficult differentiation between a squamous cell carcinoma and a keratoacanthoma requires histological sections through the entire tumor and in addition knowledge of the clinical appearance and course. Following treatment, careful follow-up is mandatory. The regional lymph node areas should sonographically be examined every 3 months for the first 2 years and every 6 months thereafter.

Functional and Reconstructive Surgery of the Pharynx Following Ablative Oncosurgical Procedures

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The prognosis of therapeutic interventions in patients with head and neck carcinomas could not essentially be improved in the last 30 years in spite of all efforts. Therefore a main goal of any therapeutic strategy is to preserve the function of the affected organs and to preserve the quality of life. In the upper aerodigestive tract the conserving functional features are swallowing, respiration and speech. To ensure these functions the surgeon has to preserve or to reconstruct the integrity of the upper aerodigestive tract. A pool of different pedicled and free microvascularized flaps can be used. Here we demonstrate pedicled and free microvascularized flaps suitable for functional reconstruction procedures of the upper aerodigestive tract by means of some characteristic clinical cases. Indications, surgical procedures, implications and complications will be discussed.

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Current Strategies of Chemotherapy – Curable and Palliative Concepts

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The role of chemotherapy in head and neck cancer is expanding in importance lately. Their usefulness is very much dependent on the stage of the disease. Chemotherapy is palliative for patients with metastatic or incurable locoregional disease. In contrast, chemotherapy in the case of non-metastatic potentially curable locoregional head and neck cancer is an integral component of a multimodality approach. In locally advanced tumors a combination of simultaneous or intermittent chemotherapy and radiation therapy has improved survival. Combination therapy even increases the median survival time in patients with inoperable tumors. Such organ conserving therapy strategies can lead to good local results without a worsening of the long term survival rate in comparison to treatment by operation alone. Several cytotoxic chemotherapy drugs have significant activity in advanced head and neck cancer when administered as single agents. The most commonly used are methotrexate, cisplatin, carboplatin, paclitaxel, docetaxel and 5-FU. No gold standard has been defined to date, although in phase III trials cisplatin shows a higher remission rate and in individual trials has also shown an improved survival rate. A higher rate of remission can be achieved through a combination of cytotoxic drugs, although two large studies have shown that there was no improvement in survival rates. Taxanes have emerged as perhaps the most active of all single agents. They have been studied in numerous combination therapies as well as in the cases of metastasized or recurrent disease. Their use in treatment has shown a high rate of remission as well as being well tolerated by patients. Taxane combination treatments without cisplatin are better tolerated and show a comparable median survival rate compared to a combination treatment containing platinum. New treatment strategies such as antibody therapy with anti-HER2/new or against the EGF receptor (IMC-C225), which are overexpressed in the majority of head or neck tumors, are currently being tested in a number of studies. Among these studies is one in which IMC-C225 in being tested as a monosubstance, in combination with cisplatin, or as a radio sensitizer. The first results indicate a significant effect, especially in the case of long term stabilization of the disease. New principles of therapy such as inhibition of tyrosine kinases together with chemotherapy will open up new treatment options in the future.

Radiotherapy for Squamous Cell Carcinoma of the Head and Neck: A Contribution to Evidence-Based Medicine

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According to the dogma of evidence-based medicine the treatment of any disease should ideally be based on sufficiently powered randomized clinical trials. A substantial number of such trials with a radiotherapy component have been conducted over time. However, many of these studies in radiotherapy as well as in other medical fields are so heterogeneous in their reporting that it is virtually impossible to judge their quality. Therefore, the reliability of their conclusions remains unclear. Recently, a new set of guidelines for reporting has been proposed. These CONSORT (Consolidation of Standards for Reporting Trials) guidelines have now been accepted by a large number of medical journals. The present review examines recently published trials according to these guidelines.
There is only one radiotherapy trial in the palliative setting. Carvalho et al [Eur Arch Otorhinolaryngol 2000] demonstrated a survival advantage of palliative radiotherapy for patients with stage IV disease compared with symptomatic treatment alone. Addition of chemotherapy did not improve survival. Radiotherapy trials in the curative setting are too numerous to be covered completely in the present review. Nevertheless a representative overview will be provided. It helps to distinguish several rationales to increase tumor cure probability, i.e. by

- increasing treatment intensity either by adding a second fraction of irradiation on some or all treatment days or by adding simultaneous chemotherapy;
- increasing the total radiation dose which has been done by increasing the number of fractions and reducing the dose per fraction (hyperfractionation);
- sensitizing resistant tumor subpopulations to irradiation;
- unspecific stimulation of the immune system via an adjuvant mistletoe treatment program.

All but the last of these approaches improve tumor cure rates at the cost of more side effects. Patients need to be properly selected for these intensified radiotherapy regimes. Also, they require expert supportive care and need to be hospitalized quite often. There is no benefit to adjuvant mistletoe treatment.

There are a number of trials addressing side effects of curative radiotherapy:

- to reduce acute mucositis by antibiotic treatment;
- to reduce xerostomia by radioprotection of salivary glands.

None of the trials on acute mucositis show any benefit of experimental over standard supportive treatment. Xerostomia can be reduced significantly. However, clinical benefit is minimal.

In summary, substantial progress has been made especially in trials based on a sound radiobiological rational.

1.1.10

Anti-Angiogenesis: A New Therapeutic Option for Treatment of Squamous Cell Carcinoma of the Oral Cavity?

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Angiogenesis is a cascade-like mechanism essential for tumor growth and metastasis. Therefore the existence of angiogenic molecules in individual tumors is of major interest. The factors or receptors most frequently contributing to angiogenesis are vascular endothelial growth factor (VEGF), Flt-1 and Tie-2. In order to evaluate the expression of these molecules in the sera of patients with squamous cell carcinoma of the oral cavity (SCCOC) and to assess their potential as prognostic marker the following study was initiated.

Serum levels of VEGF, Flt-1 and Tie-2 were assayed by ELISA technique in 51 patients with untreated SCCOC and 10 healthy controls. All levels were determined preoperatively, 24 hours, 1 week as well as 2, 3, 4, and 5 weeks postoperatively. Statistical evaluation was performed using Mann-Whitney, Kruskal-Wallis and Wilcoxon tests.

Serum levels of VEGF, Flt-1 and Tie-2 were not significantly raised in patients with SCCOC and there was no association with either tumor stage or presence of nodal metastases. Furthermore, no statistical correlation was found between serum levels of VEGF, Flt-1 and Tie-2 and microvessel density assessed by immunohistochemical staining of tumor specimen with a CD31 antibody.

Our study indicates that serum VEGF, Flt-1 and Tie-2 measurements are of little practical use as an initial or additional diagnostic tool in case of SCCOC.

1.1.11

Gene Therapy: Therapeutic Exploitation of the p53 Pathway

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Squamous cell carcinoma represents ~90% of all head and neck cancers, with an incidence of 500,000 cases worldwide [1]. Present therapy of head and neck cancer patients includes surgical procedures, radiation therapy, and chemotherapy. Despite the evolution and refinement of multimodal treatments for head and neck cancer, over recent decades no dramatic improvements have been obtained with respect to efficacy and associated morbidity of these patients [2]. However, based on our increasing knowledge of molecular biology, immunology, biochemistry and biology of head and neck squamous cell carcinoma (HNSCC), new perspectives on therapy are arising. Among other approaches, gene therapy and immunotherapy are attracting most attention.

At present, it is widely accepted that cancer arises as a result of the accumulation of genetic alterations in oncogenes and tumor suppressor genes, followed by clonal evolution. The most frequent genetic alterations in HNSCC are losses of 3p, 5p, 8q, 9p, 13q, 18q and 21q and gains of 3q, 7p, 8q, 9q, 11q and 20q. Hence, these tumor cells harbor specific clonal genetic changes that can be therapeutically targeted.

Mutations in the p53 gene, which is also described as the ‘guardian of the genome’, occur in 50% of all human cancers, highlighting the central role of p53 as a tumor suppressor gene [3]. The p53 gene is a transcription factor, that controls the expression of a large panel of proteins involved in growth control, DNA repair, cell cycle progression, angiogenesis, metastasis, and apoptosis [4,5]. Molecular studies have shown that mutations in the p53 gene can be divided into at least three distinct classes with respect to conformational alteration, core-domain folding and tetramerization. Over 1700 different mutations in p53 have been reported, interestingly many of these mutations are missense mutations. Based on the myriad of p53 downstream targets and different p53 mutations numerous strategies are implicated in treatment of tumors harboring a p53 mutation.

The purpose of this presentation is to highlight the therapeutic exploitation of the p53 pathway with particular relevance to the treatment of head and neck cancer.

1.2 Psychooncology

1.2.1 Psychotherapy of Cancer Patients. What is Empirically Supported?

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Prospective course studies of cancer diseases show that emotional and social factors like depression, helplessness, suppression of feelings and social isolation have a negative influence on the course of the disease. Active coping with the disease and lack of social support may have a positive influence. Over the past 20 years, a series of psychotherapeutic interventions have been developed which might have improved the patient’s emotional well-being and quality of life. Patients receiving psychotherapeutic help showed less anxiety and depression, were better able to solve problems and had more adequate ways of coping with the disease. They had more confidence in medical treatment, showed greater willingness to cooperate and complied better with regimens.

It is consensus that a psychotherapeutic program of treatment must be offered in various steps. The first step provides information and consultation concerning the relationships between psychosocial support of cancer patients and psychoeducative techniques for modification of health-destructive behaviors like smoking, lack of exercise, unhealthy eating habits. The second step covers learning of coping mechanisms including relaxation techniques, hypnosis, meditation and imaginative techniques for treating disease-related symptoms like pains, nausea and vomiting. The third step deals with specific cognitive-behavioral therapeutic approaches for reduction of anxiety and depressive symptoms, and psychodynamic based procedures for dealing with existential questions and working out of problems in partnership, on the job, or in the parent-child relationship.

Both psychoeducation and behavior training, single and group psychotherapy, and the including of partners and persons close to the patient have been found empirically effective. Specific psychotherapeutic interventions in step 3 are indicated for ca. 20–30% of patients. There are no differences between the various therapy concepts. Studies which postulate a positive influence of psychotherapeutic interventions on the course of disease and the survival times of cancer patients have been found empirically effective. Specific psychotherapeutic help showed less anxiety and depression, were better able to solve problems and had more adequate ways of coping with the disease. They had more confidence in medical treatment, showed greater willingness to cooperate and complied better with regimens.

1.2.2 Quality of Life: A New Outcome Criterion in Oncology

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In the early seventies of the last century the concept of quality of life has been taken up in medicine. Within the last decades, its significance in clinical practice and research have grown up which can be documented by the increasing publication rates per year. To distin-
functions or psychomotoric performance, what reflects the lack of a consistent pathophysiological model for possible adverse effects of the disease itself and/or the oncological treatment on the CNS and the impairments in cognitive functioning caused by that. Recently, neuropsychological assessment has been focused more on aspects of attention as basic deficits caused by chemotherapy. This has also lead to more differentiated and theory-based diagnostic strategies. A number of studies showed that self-evaluation of patients regarding their current level of cognitive functioning did not correlate with data from formal neuropsychological assessment. Complaints about cognitive problems were strongly correlated with aspects as anxiety, depression, and also fatigue. On the other hand, the validity of neuropsychological assessment is surely limited, as we are confronted with subtle deficits and in most of the cases we have no reference data from neuropsychological assessments before tumor diagnosis which makes it difficult to assess the premorbid status of cognitive capacities. Besides this there are many further factors having possibly negative implications on cognitive functioning. This illustrates the need for multidimensional diagnostic and therapeutic strategies. The presentation will cover the most important empirical data on the issues described above and try to give suggestions for strategies in further research on the topic.

1.2.4 Psychosomatic Liaison Service Delivery in Oncology: Possibilities and Limitations

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Currently the need for psychosocial care delivery in oncology is well accepted. Patients are frequently demanding psychosocial help as part of their treatment. In general hospitals psychosomatic consultation and liaison services are responsible for the psychological care of patients and their relatives as well as for the counseling of physicians and nurses in psychosocial questions. Based on their different conceptual structures the liaison service delivery involves a stronger integration of the psychooncologist in the medical setting compared to the care delivery by consultation services. Due to the more intensive cooperation, the early referral of patients in need and the timely utilization of psychosocial interventions the liaison model is frequently experienced as more satisfying and effective. Liaison service delivery is time consuming and staff intensive for both, the psychooncologists and oncologists: Therefore this concept is implemented in medical units which are extremely traumatic and stressful for patients and their relatives as well as for medical staff, for example in bone marrow or stem cell transplant (BMT/SCT) units.

A psychooncological cooperation exists between the Department of Hematology/Oncology and the Department of Psychosomatics and Psychotherapeutic Medicine at the university hospital of Freiburg for more than eight years. This includes a psychooncological liaison service on the BMT/SCT unit for several years. Based on systematic case documentation relevant characteristics of patients and psychooncological care delivery will be described. The possibilities and limitations of care delivery by liaison services are demonstrated. Finally, the demands on an effective psychooncological care of high quality under the perspective of the actual changes in German health care system are discussed.

1.3 The Patient with Metastatic Disease

1.3.1 The Patient Suffering from Metastases

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The principle of choice in the treatment of patients with metastatic disease is ‘nihil nocere’. Palliative treatment means on the one hand systemic therapy to reduce the progress of the metastases or on the other hand it can be ‘aggressive’ in terms of surgery or radiotherapy (Bleeding, Osteolysis, fracture). For the appropriate extend of therapy it is necessary to know the actual state of disease. Aggressive or invasive treatment should only be given at those sites, where it is really needed.

Systemic – possibly toxic – therapy is required, when progress of disease can be reduced. In case of non symptomatic progress of metastases aggressive chemotherapy should not be applied; the intend to treat has to be clearly defined before any therapeutic activity. In addition to the above mentioned procedures, drug therapy for the reduction of pain or the treatment with radiopharmacas might be useful.

Treatment of patients with metastases is a multidisciplinary approach.

1.3.2 Palliative Radiotherapy in Patients with Disseminated Tumors – the Example of Bone Metastasis

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In patients suffering from advanced tumors radiotherapy offers various possibilities of palliative symptom control. As an example this is reported for bone metastasis.

Bone metastasis: Many advanced tumors tend to develop osteolytic or osteoplastic bone metastasis which are the most frequent indication for palliative radiotherapy (~ 60%). Diagnostics: In a patient with a histologically known tumor and with pain in some bone area, as first line diagnostics a bone scintigraphy should be done. Additionally X-rays of suspicious areas should be performed. In many cases this may be a sufficient diagnostic effort. But especially in the vertebral column stability of the bone must be checked and danger of a fracture must be excluded. This should be done by CT-scan. Besides it might be useful to find an infiltration of other than bone tissue by MRI. Therapy: If operable, patients with non-stable bone metastasis (danger of a fracture) or patients with symptoms of the spinal cord should be operated to stabilize the bone before radiotherapy. After operation adjuvant radiotherapy is indicated. In patients with stable but symptomatic bone metastasis or inoperable patients radiotherapy should be started as soon as possible. Radiotherapy of bone metastasis is used to improve or conserve quality of life with two basic aims: control of pain and new stability of the bone. When choosing one of these aims prognosis of the disease and general condition of the patient should be considered. To reach control of pain some days or weeks, to reach bone stability some months are needed. The fractionation and the duration of the radiotherapy course can be changed considering the aim of therapy. One single dose of 8 Gray is highly sufficient to get a good control of pain. To reach the aim of bone stability and a long time of pain relief a fractionation of 5x3 Gray per week with a total dose of 30 Gray or 5x2 Gray per week with a total dose of 40 Gray is needed. Pain relief can be reached by radiotherapy
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1.3.3 Patients with Metastases – Therapeutic Options with Bisphosphonates

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Bisphosphonates have been used successfully for many years in the treatment of cancer-induced hypercalcemia, Paget’s disease and postmenopausal osteoporosis. In addition, inhibition of osteolysis by bisphosphonates has been shown to be highly efficient as an adjunctive therapy for the delay or prevention of cancer-related skeletal morbidity.

Experimental evidence indicates that the development of bone metastases from breast cancer and multiple myeloma is facilitated by the release of substances from tumor cells such as interleukin-1, interleukin-6 and tumor necrosis factor that activate osteoclasts to cause local osteolysis. Clinically the increased osteoclastic activity leads to pathologic fractures, hypercalcemia and pain. Bisphosphonates as pyrophosphate analogues have high affinity for bone and are preferentially delivered to sites of increased bone formation or resorption. Once deposited on the surface of bone, bisphosphonates are ingested by osteoclasts that are engaged in bone resorption. Several animal models, as well as a number of cell culture experiments, indicate a prophylactic effect of bisphosphonates in respect of subsequent bone metastasis and have provided the preclinical background for the adjuvant use of bisphosphonates in primary cancers. Bisphosphonates exert apoptotic and anti-proliferative effects on osteoclasts. In addition, recent in vitro data indicate that bisphosphonates inhibit the attachment of breast and prostate cancer cells to bone matrix and enhance apoptosis also in myeloma and breast cancer cells.

In agreement with these experimental data, bisphosphonate are now widely used therapeutic agents for bone metastases in patients with breast cancer, multiple myeloma and prostate cancer. In patients with established bone metastases from breast cancer, clodronate or pamidronate has been shown to reduce the incidence of hypercalcemia and pathologic bone fractures. Moreover, in patients with relapsed breast cancer without obvious bone involvement, clodronate significantly reduces the subsequent risk of bone metastases. Similarly, in breast cancer patients with no clinical evidence of metastases, but with cancer cells detected in the bone marrow, clodronate has been reported to reduce the incidence of bone metastases. Increasing evidences indicate that despite the osteoblastic nature of metastatic bone lesions due to prostate cancer osteolysis is a regular feature and may cause skeletal morbidity. Bisphosphonate treatment of painful osseous metastases due to hormone refractory prostate cancer results in a significant pain decrease and a significant decrease in the daily consumption of analgesics in the majority of patients.

Overall, the results of adjuvant therapy regimes including bisphosphonates are promising but need confirmation in further studies. Specifically, initiation of therapy and optimum period of treatment, specific drug, dosage and route of application need to be determined for each tumor entity in randomized clinical trials.

1.3.4 Neurosurgery of Brain Metastases

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Brain metastases are common in patients with systemic cancer and almost invariably lead to death if not treated. The aim of therapy however is not only tumor-control but mostly preservation of life quality, by keeping the patient as long as possible symptom-free. Most brain metastases become overtly symptomatic and lead to inexorable neurologic symptoms including: headache, limb paresis, behavioral and cognitive changes, and seizures.

Early symptoms caused by peritumoral edema can be sufficiently treated with glucocorticosteroids. Specific treatment modalities include microsurgical removal, radiosurgery and radiotherapy. The choice of therapy depends on the general clinical condition of the patient, the localization and the size of the tumor, but also on the number of cerebral foci and the systemic dissemination of the disease. Treatment of choice for brain metastases with masseffect is surgical resection followed by postoperative radiotherapy. In case of small deep seated lesions stereotactic radiosurgery is preferred.

Although prompt diagnosis and vigorous treatment of cerebral metastases may lead to remission of symptoms, enhance quality of life and even prolong survival, the treatment modalities remain primarily palliative and need to be discussed interdisciplinary and in direct contact with the patient and his social environment.

1.3.5 Whole Brain Radiotherapy for Everybody? Prognostic Factors and New Developments in the Treatment of Patients with Brain Metastases

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The prognosis of patients with brain metastases is extremely poor. Median survival is about 4 months. The Radiation Therapy Oncology Group (RTOG) has recently proposed a prognostic classification which is presented and discussed in this talk. The purpose is especially to validate this model for patients with the worst prognosis as they form the largest group in clinical practice.

916 patients with brain metastases had resection and whole brain radiotherapy (WBRT, n = 257) or WBRT alone (n = 659) at our institution from 1985 until 2000. Patients were grouped into RPA classes 1, 2, and 3 (n = 67, 441, and 408, respectively).

Median survival of the whole group was 3.4 months. Median survival in classes 1, 2, and 3 was 8.2, 4.9, and 1.8 months, respectively. In class 3, age (<65 years vs. ≥65 years, relative risk [RR] 0.75), status of the primary tumor (controlled vs. uncontrolled, RR 0.86), and the number of brain metastases (single vs. multiple, RR 0.76) were independent prognostic variables. We defined three prognostic subgroups: Class 3a (n = 51): age <65 years, controlled primary tumor, single brain metastasis; class 3c (n = 44): age ≥65 years, uncontrolled primary tumor, multiple brain metastases; class 3b (n = 313): all other patients. Median survival in classes 3a, 3b, and 3c was 3.2, 1.9, and 1.2 months, respectively (p < 0.0001). Intra-class comparisons showed that resection followed by whole brain radiotherapy yielded significantly better survival compared with whole brain radiotherapy alone. Our results validate the RTOG RPA classification for patients with brain metastases. The variables age, status of the primary, and num-
Nutritional Care

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The detection of metastases in the process of a cancer disease also means a palliative intent for the nutritional care of the patient. Because palliative stage contains different phases with different prognosis and thereby different targets, they are no general guidelines for nutritional treatment. Nutritional methods during rehabilitation, when many patients are in good performance and the targets are recreation and conservation of independence and ability, are more aggressive than in the final time, where the palliation of symptoms has priority. Weight loss and malnutrition many occur in every phase of a malignancy and are already present at the time of diagnosis in 50% of the patients. Most severe weight loss, characterized as cachexia, consists of loss of muscle and fat mass with compensatory gain of body water. The degree is unrelated to the different kinds of cancer, low in hematological malignancies, breast cancer and sarcoma and in 54–64% detectable in patients with lung cancer, colon cancer and prostate cancer as well as in more than 80% of patients with pancreatic and gastric cancer. With progression of the malignancy 80% of the patients are suffering from anorexia, nausea and emesis with at the same time raised energy expenditure. The consequence is a progressing loss of protein and fat reserves with increasing fatigue and apathy. Main causes are cancer induced metabolic alterations of the protein – fat – and carbohydrate metabolism, which are different from the metabolic alterations in hunger metabolism and impair the efficacy of nutrient utilisation. Mediators of this alterations are considered to be cytokines released from patient, also cancer specific products acting peripheral and central. Because malnutrition significantly affects morbidity and mortality and mainly the quality of life of the cancer patients, nutritional interventions are also important in palliative supportive care. They aim to minimise loss of muscle mass and thus maintain reserves of activity and quality of life. The following nutritional actions should be used individually with simultaneous consideration of the nutritional state, additional diseases, the oncological treatment and the clinical status of the patient. If possible, oral nutrition is favoured according to the individual needs of the patient offered as ‘nutrition satisfying the desires’. Thereby the offer of industrially made formula diets and supplements may be helpful. No abstinence should be made from the different possibilities of enteral and parenteral nutrition as long as the needs of the patient are thus satisfied and his quality of life encouraged. Concerning the supply of nutrients in oral nutrition, the guidelines of a healthy nutrition have no priority, especially not concerning problems during oncological treatment. The patient composes the meals according to his desire. The enteral and parenteral nutrition are individually composed according to the nutritional guidelines with regard to the energy requirement of the patient (bedridden, mobile patient), loss of nutrients (emesis, diarrhoea) as well as other diseases respectively organ insufficiencies. The recommendations for the supply of amino acids are 1.0–1.5 g protein /kg/d (liver insufficiency with amino acid intolerance 0.6–1.0 g protein /kg/d; renal insufficiency 0.8–1.5 g protein /kg/d depending on BUN-rise), for carbohydrates max. 5 g glucose /kg/d and for fatty acids 0.8–1.5 g/kg/d.

1.4.1 Epidemiology and Typing of Thyroid Carcinomas

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1. Etiology and epidemiology
Cervical irradiation and heredity have been proven to be risk factors for the development of thyroid carcinomas.

Irradiation:
On April 26 in 1986 the nuclear reactor in Chernobyl Ukraine was destroyed by an explosion. This accident was followed by an uncontrolled liberation of marked amounts of radioactivity (particularly 131 J and 133 J). Due to the southwest, the main radioactive fallout was registered in the city of Gomel (Belarus). As one of the grave effects of this irradiation, newly occurring carcinomas of the thyroid gland were observed in the group of children younger than 15 years. Between 1994 and 1997 the incidence of thyroid cancer of this population in the a.m. region increased to the 9.5 fold compared with the 4 years period before the Chernobyl accident.

Inherited factors:
Partly, medullary carcinomas of the thyroid show an autosomal dominant heredity mainly representing the inherited Multiple Endocrine Neoplasia (MEN) type II.

2. Classification of carcinomas
Histological typing of World Health Organization (WHO, 1993) includes the following classification of primary thyroid carcinomas:

Follicular carcinoma,
Papillary carcinoma,
Medullar (C-cell) carcinoma,
Undifferentiated (anaplastic) carcinoma.

Follicular carcinoma (ICD-O-8330/3):
Follicular carcinoma shows the evidence of follicular cell differentiation, lacking the diagnostic features of papillary carcinoma.

Following the cytological diagnosis of a ‘follicular neoplasia’ of the thyroid, the histological decision whether the lesion is a follicular carcinoma or adenoma, should never be made with a frozen section because of the inaccuracy of this technique to exclude infiltrative growth in the area of tumor capsule.

The biological behavior of the tumor depends upon the age of patients (better prognosis in human beings under 45 years), its stage grouping and upon its histopathological features.

Prognostically, the following subtypes according to their degree of invasiveness are classified: minimally invasive (encapsulated) and widely invasive (often lacking complete encapsulation). Furthermore, two cytological variants can be distinguished: oxyphilic cell type (malignant oncoytoma) as well as clear cell-type.

Depending on the a.m. features, follicular carcinomas show moderate to worse prognosis. These tumors prefer haema-togenous metastasizing (lung and osteolytic skeletal metastases). All patients with hypercellular carcinomas of follicular origin including the oxyphilic variant, should be observed with care because of the worse prognosis of these neoplasias.

Using immunohistochemistry, follicular carcinomas show an obligato expression of thyroglobulin, often also of vimentin.

Papillary carcinoma (ICD-O-8260/3):
Papillary carcinoma exhibits follicular differentiation, and in addition papillary and follicular structures as well as characteristic nuclear changes.

1.4 Endocrine Cancer
Depending on their different growth pattern, the following variants can be distinguished:

- Papillary microcarcinoma is defined as a papillary tumor 1 cm or less in diameter.
- Encapsulated variant of papillary carcinoma
- Follicular variant of papillary carcinoma may be composed entirely or almost of follicular structures. Apart from the absence of typical papillae, these tumors resemble papillary carcinoma in their morphological, particularly in their nuclear features as well in their clinical behaviour.
- Diffuse sclerosing variant; these rare papillary carcinomas show a diffuse involvement of one or both thyroid lobes exhibiting dense sclerosis and psammoma bodies within the papillary proliferation.
- Carcinomas with oxyphilic cell type are rare thyroid neoplasias. Regarding the biological behavior, the papillary carcinoma of thyroid provides the most favorable prognosis. Depending on the age of the patient (younger than 45 years with better, older than 45 with worse prognosis), on the stage grouping of the tumor and on its histological growth pattern, the papillary carcinoma has an excellent to moderate prognosis. Papillary carcinoma predominantly metastasizes into lymph nodes, particularly into the regional (i.e. cervical) nodes.

Medullary (C-cell) Carcinoma (ICD-0-8510/3):

A carcinoma showing evidence of C-cell differentiation. In most tumors stromal amyloid is present. This tumor is counted among the neuroendocrine carcinomas (originating from the APUD system) typically exhibiting an expression of calcitonin, of neuroendocrine markers like chromogranin, and often also of the Carcinoembryonal Antigen (CEA) by immunohistochemistry. Depending on its stage, the medullary carcinoma of the thyroid shows a moderate to poor prognosis, the latter being typical for the inherited variant. Metastases do not only occur in lymph nodes but also as distant metastases predominantly in liver and paranephals.

Undifferentiated (anaplastic) carcinoma of the thyroid (ICD-0-8020/3):

- A highly malignant carcinoma which is composed mostly of undifferentiated cells.
- Cytologically, the large-cell anaplastic carcinoma must be distinguished from the small cell variant (DD Non-HODGKIN lymphomas).
- Anaplastic carcinoma of the thyroid is one of the most malignant human tumors. 60% of patients bearing this neoplasia die within the first 6 months following diagnosis. This highly malignant neoplasia mostly occurs in older patients, typically showing a destruction of cervical tissue as well as lymphogenous and hematogenous metastases.

TNM Classification:

Stage of thyroid carcinomas is performed due to the definitions of UICC (2002). The pTNM system gives a description of tumor extension (T), of lymph node metastases (N), and of distant metastases (M). Regional lymph nodes are the cervical and upper/superior mediastinal nodes.

Thyroid metastases of tumors from extrathyroid origin

Lung and renal carcinomas are frequently observed to metastasize into the thyroid gland.

References:

a thyroid malignancy with a probability of 95% and avoids surgery with a subsequent histological examination. Using FNB as a normal routine procedure to determine the nature of hypoechogenic and cold nodules the morbidity of thyroid diagnostics can be minimized. Small and not-palpable nodules should be punctured using US guidance and control. It is advisable to take an image for documentation showing the needle’s tip located correctly in the center of the lesion. The complication rate of FNB is very low, if a coagulation disorder is excluded. Unfortunately FNB is not applied in the necessary and possible frequency in Germany.

1.4.4
Thyroid Cancer – Radiotherapy

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Thyroid carcinoma is a rare disease in the general population. The prognosis varies widely among the histological subgroups. Surgery is the most effective treatment but in some subsets radiotherapy is important as well. Differentiated thyroid carcinomas are considered to be more radiosensitive than medullary, intermediate, and anaplastic carcinomas. Since the anaplastic thyroid carcinoma is one of the most aggressive neoplasms affecting humans, radiotherapy is basically suggested either for unresectable, palliative or resected tumors. According to symptoms, stage and patient’s condition 45 up to 70 Gy are delivered. Concurrent chemotherapy should be considered since retrospective studies recently reported on a successful employment of multi-modality treatment.

In medullary carcinoma, thyroidectomy with neck dissection is recommended by most authors either for primary or secondary lesions. Patients with initial large tumor volume, R1-2 resection, T4 or unresectable tumors and with large lymph node involvement, respectively, are referred to radiation. The region at risk should be treated with 60-70 Gy.

About 70% of malignant tumors of the thyroid gland are of the well-differentiated papillary, follicular or mixed histological types that have a good prognosis, but even these as well as the medullary and anaplastic tumors differ varying in their malignant potential. Combined cancer treatment includes surgical removal of as much malignant tissue as possible and radioidine therapy for residual disease. External beam radiation is employed for the local regional control. It is recommended for patients with T4 tumors, R1 or R2 residual resection or individual risk factors as male gender, follicular carcinoma, grading III and age more than 45 years. In 1995 the “Freiburger Konkenssuss” paper was published, suggesting postoperative radiation treatment for differentiated tumors of the stages pT4 pN0-1 R0-2. Radiotherapy in pT1-3 tumors with lymph node involvement should be decided individually.

Metastases: Resection and radioiodine therapy should be considered in distant metastases of differentiated carcinomas. Radiotherapy is recommended for bone and brain metastases as well as for mediastinal lymph nodes causing dyspnkea and disphagea. Technique: 3D conformal CT-planning is required for external beam radiation. Both photons and electron beams of an linear accelerator are used to fit the target volume. Both sides of the neck from the hyoid to the supraclavicular fossae and the mediastinum down to the carina are irradiated in a 5 to 9 field-technique. With the spinal cord, the lung and the floor of the mouth being shielded, a dosage of 50 to 70 Gy is delivered in daily fractions of 2 Gy.
1.4.5 Thyroid Cancer – Follow Up

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All thyroid cancer patients must be treated with thyroid hormones (levo-Thyroxine = L-T4) after thyroidectomy, irrespective of its extent. There are two reasons for this treatment: 1. To correct surgical-induced hypothyroidism and 2. To suppress stimulated growth of persistent or recurrent neoplastic disease by reducing TSH levels. L-T4 treatment is a life-long therapy and should be adapted to each patient according to the clinical status. Adverse effects of the L-T4 therapy are minimal (heart, bone). The follow-up program should be performed risk-adapted and life-long. A basic examination should be performed every 6 months and after 5 years once a year. The basic examination should include: history taking, serum thyroglobulin measurement (tumor marker), clinical and ultrasonographic examination of the neck. A 131iodine total-body scan (131I-TBS) should be performed 3–4 months and about 1 year after radioiodine ablation therapy. For patients belonging to the ‘high risk’ group a 131I-TBS may be indicated yearly or every second year. When a pathologically elevated thyroglobulin level is noticed, further examinations can be used to localize the recurrence or the metastases: 131I-TBS, X-rays of the chest, ultrasonographic examination of the abdomen, CT scan of the neck and chest, MRI of the neck, 18F-FDG-PET, skeletal-sciintigraphy.

Medullary thyroid carcinoma: After surgical therapy a hereditary disease should be excluded by molecular genetic testing. Other endocrinological diseases should be carefully evaluated (pheochromocytoma, primary hyperparathyroidism). The follow-up program includes the measurement of serum calcitonin and carcinoembryonic antigen (CEA) values (tumor marker). Further examinations should be performed when the tumor markers are elevated: 18F-FDG-PET, 18F-DOPA-PET, 111In-Octreotid-sciintigraphy, MRI of the abdomen.

1.5 Future Prospects of Patho-Histological Diagnosis

1.5.1 Is the Quality of a Pathologic Diagnosis Dependent on Electronic Image Transfer or Not?

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Among the various t tempted applications such as frozen section service this cannot be obtained by a local pathologist and is performed by either the surgeon himself or a trained technician who gets support via videoconferencing by the remote pathologist. Microscopic selection of regions of interest is pivotal as well. In telepathologic frozen section services a technician is either instructed to navigate through the slide or using remote controlled microscopes the pathologist is able to select the fields and magnifications by himself. This set up enables frozen section services to be undertaken in regions out of physical reach of a pathologist. Many studies have shown that diagnostic quality is as good using well -trained technicians instructed by video conferences with the pathologist as compared with in-house services.

Concerning expert consultation services the accuracy of the diagnosis is again highly dependent on the selected images. Thus, focusing on specific regions neglecting others can lead to completely different diagnoses. This time the ‘non-expert’ pathologist is selecting the areas of interest without being influenced by the expert, who has to make his diagnosis upon this and additional (e.g. clinical, laboratory) data, though he might request or suggest additional stains to narrow the diagnostic possibilities. Several internet-based consultation services have been established (e.g. iPath server in Basel, UICC-TPCC in Berlin), are now-a-days numerous pathologists are skeptical regarding the quality and accuracy of this field.

Diagnostic quality in the field of pathology is extremely dependent on the selected area of the specimen and the preparation of the slide and their stains. This is why macroscopic specimens are dissected by pathologists, who choose the areas of interest. In telepathology applications such as frozen section service this cannot be obtained by a local pathologist and is performed by either the surgeon himself or a trained technician who gets support via videoconferencing by the remote pathologist. Microscopic selection of regions of interest is pivotal as well. In telepathologic frozen section services a technician is either instructed to navigate through the slide or using remote controlled microscopes the pathologist is able to select the fields and magnifications by himself. This set up enables frozen section services to be undertaken in regions out of physical reach of a pathologist. Many studies have shown that diagnostic quality is as good using well -trained technicians instructed by video conferences with the pathologist as compared with in-house services.

1.4.6 Medullary Thyroid Cacinoma and Parathyroid Carcinoma

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Medullary thyroid carcinoma (MTC) originates in the parafollicular cells (C cells) of the thyroid, secreting both calcitonin and CEA. Prognosis and treatment effectiveness of medullary thyroid carcinoma are largely related to the tumor stage, so that early diagnosis represents an important goal for the management of patients. Recent advances in genetic testing have improved the clinical approach to the familial MTC syndromes. Sporadic MTC usually presents as a solitary palpable thyroid nodule and in most cases the definitive diagnosis is established only at the time of surgery. The goal of primary operation for MTC is complete removal of the neoplastic tissue, because any adjuvant treatment has never been proven to be effective. The management of residual/recurrent or metastatic MTC still remains controversial, although a multimodal approach to advanced disease may be of value in palliation or local control of tumor progression. Although parathyroid neoplasms are common and cause primary hyperparathyroidism, parathyroid carcinoma is a rare entity. Patients with parathyroid carcinoma usually present with profound symptoms of hyperparathyroidism and highly elevated serum calcium and parathyroid hormone (PTH) levels. At the time of neck exploration, a large, gray-white, locally invasive tumor is commonly encountered. The course of patients with parathyroid carcinoma is variable; unfortunatly, more than 50% have persistent or recurrent disease due to regional or distant disease. Surgical resection is the principal treatment for patients with parathyroid carcinoma. The optimal surgical treatment is en bloc tumor resection with ipsilateral thyroid lobectomy when the diagnosis is suspected. Patients who have persistent or recurrent parathyroid carcinoma should have localizing studies to identify loco-regional or distant tumor sites. Re-operation in patients with localized parathyroid carcinoma is recommended because it relieves symptoms of hypercalcemia, and it normalizes serum calcium and PTH levels in most patients. For patients who have unresectable parathyroid carcinoma, a protocol-based treatment with chemotherapy and external radiotherapy should be considered. Additionally, second-generation bisphosphonates and the NPS R-568 calcimimetic agent may be useful in normalizing the serum calcium and improving symptoms of hypercalcemia. However, they do not treat the tumor and are rarely effective in the long term.
1.5.2 Disseminated Tumor Cells and Minimal Residual Disease: Diagnosis and Prognosis

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The issue of tumor cell dissemination (minimal residual disease, MRD) in patients with solid tumors manifesting itself by the presence of disseminated isolated tumor cells in blood, bone marrow and other tissue samples recently became a widely discussed subject in respect of prognosis of the disease and monitoring the response to therapy. Accurate detection of disseminated tumor cells requires tumor specific target molecules which allow sensitive and specific assays and preferably enable to quantification. Disseminated tumor cells and MRD can be detected by a series of techniques, including immunocytochemistry, polymerase chain reaction (PCR), fluorescence in situ hybridization, flow cytometry, clonogenic cultures and, recently, immunomagnetic procedures. These methods differ in the identification of targets, they have varying sensitivity and specificity and different advantages and disadvantages. So far a wide variety of tumors have been investigated including gastro-intestinal, colorectal, pancreatic, lung, prostate and breast cancer with varying sample sources being examined. In not all but several tumor entities the detection of disseminated tumor cells (minimal residual disease) can function as an independent significant determinant in respect of relapse, disease free and overall survival and correlates with parts of the UICC-Classification system. In this overview we intend to summarize the methods used for detection and characterisation of disseminated tumor cells and point out the prognostic significance and eventual clinical implications.

1.5.3 Cancer Metastases of Unknown Origin (CUP): Diagnostic Approach

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Cancer metastasis of unknown primary site represent one of the most complex fields of surgical pathology, making their adequate classification a real challenge. In such cases a proper diagnosis can often not be made on routine histological stains but requires additional techniques. Immunophenotypic and genotypic analysis are useful adjuncts to provide insights into the histogenesis and may indicate the tissue of origin. Immunophenotypic profiles are easily obtained by panels of commercially available antibodies. Currently, they may be applied to formalin-fixed paraffin-embedded tissues sections when antigen-retrieval techniques are used. It is well known that different human tissues are characterized by the expression patterns of certain polypeptides which may be retained in the corresponding carcinoma types. However, the expression of additional proteins may be switched on or characteristic genes may be repressed in the event of malignant transformation and tumor progression. A phenotypic shift may in part also result from epigenetic factors or the influence of the microenvironment. Thus, aberrant staining profile may be observed in neoplasms when compared to the tissue of origin. In spite of these pitfalls, a correct histopathological classification can be obtained in many cases and lead to a specific treatment modality. In order to save laboratory and financial resources, a narrow primary antibody panel may first be chosen which focuses of the discrimination between broad categories, i.e. undifferentiated carcinomas versus lymphomas. They are followed by secondary more specific panels which may help to further designate the exact entity. The immunohistochemical analysis of lymphomas includes lineage-, differentiation-, and subset-associated antigens, fusion proteins resulting from chromosomal translocations and cell-type characteristic transcription factors. Genetic studies demonstrating characteristic translocations or mutations may further contribute to the final diagnosis. The subclassification of carcinomas usually includes the identification of cytokeratin subtypes, especially the CK20+/CK7- profile. Additional well established markers are estrogen receptor (particularly, but not exclusively breast, endometrial and ovarian tumors), prostate specific antigen (prostatic cancer), hepatocyte antigen (hepatocellular carcinoma), CA125 (serous and endometroid adenocarcinoma of endometrium and ovary, adenocarcinoma of lung), TTF-1 (thyroid cancer and nonsquamous cancer of lung), synaptophysin (neuroendocrine tumors). Additional immunophenotypic and genetic studies are proposed when mesotheliomas, melanomas, germl cell, soft tissue, neural or ‘small, blue, round cell tumours’ are suspected.

1.5.4 An Outlook on Molecular Pathology

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‘Molecular pathology’ can be broadly defined as the use of genetic data, in addition to the standard pathological parameters, to optimise diagnosis and to indicate treatment and prognosis. The benefit to be gained from the exploitation of molecular techniques to provide additional information to aid patient management is potentially vast. In the last two decades molecular techniques have significantly contributed to our understanding of the function, differentiation and oncogenesis of preneoplastic cells as well as tumor growth and biologic behavior of tumors. This overview deals with molecular methods, which are applied in-situ to identify DNA, specific mRNAs and chromosomal structures at a cellular level, such as in-situ hybridization (ISH) and fluorescent in-situ hybridization (FISH). We also focus on liquid based molecular methods, which are applied in molecular pathology. They include microdissection of cell groups or single cells for molecular analyses, polymerase chain reaction (PCR) based methods for DNA and RNA detection as well as the analysis of mutations, loss of heterozygosity and clonality. Furthermore, comparative genomic hybridization (CGH) and the array technology to identify chromosomal gains and losses as well as gene expression are discussed. Thus, these new technologies will have an enormous impact in molecular pathology with several diagnostic, prognostic and therapeutic implications.

1.5.5 Is it Possible to Predict the Response of Tumors to Therapy?

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The success of anti-cancer therapy is hampered by two major points, namely the highly heterogeneous nature of tumors, between and within tumor entities, and the complex network of interacting pathways in tumor development and progression. Not surprisingly, most
therapeutic regimens fail to achieve a positive response in all treated patients. Identification of factors predicting the response to a given therapy would therefore stratify patients that will or will not benefit from the therapy as well as to exclude patients with a higher risk of toxic side effects.

Clearly, one has to discuss the question of response prediction to therapy with respect to 1) the type of therapy and associated marker, 2) the accessibility and type of tissue material and 3) the disease time point. First, for those anti-cancer agents with a single, well defined (molecular) target or pathway, response prediction may be possible with a specific marker or marker panel. The novel therapeutic approaches for breast and colon cancer or myeloproliferative disorders may serve as examples. In contrast, for other therapies, which unspecified target a broader range of interacting cells and tissues (e.g. radiation, multi-agent chemotherapy), response prediction is more difficult. Second, the selection of tissues (resection specimens, biopsies, circulating body fluids) as well as the respective laboratory methods (imaging, molecular) for analysis of predictive molecular markers may influence sensitivity and specificity. Finally, a single time point may not suffice for defining the status of a predictive marker and a restricted monitoring may be more informative. Nevertheless, with the growing knowledge of tumor biology and novel investigative tools, response prediction may be one of three key aspects (early detection, response prediction and monitoring) of individual patient care, especially if one deals with a well defined tumor entity, a highly selective marker and a sensitive and specific procedure.

1.5.6 cDNA Arrays – a Useful Diagnostic Tool in Pathology?

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The high density micro array technology allows screening expression levels of a large number of genes in order to detect transcription levels under various conditions. A cDNA array consists of thousands of oligonucleotides or cDNAs of known sequences that are immobilized on a substrate. RNA isolated from a tumor is reverse transcribed into cDNA and the cDNA is labeled with a fluorescent dye. Similarly, RNA isolated from a normal reference sample is reverse transcribed into cDNA and labeled with another fluorescent dye. Both cDNA pools are hybridized to the arrays and the resulting fluorescence values reveal the relative levels of RNA transcripts in the tumor, compared to the reference sample using mathematical algorithms. This “fingerprint” of the genes expressed by the tumor will be useful in future to subclassify morphologically homogeneous tumors into subgroups that show different biological behavior and responses to specific therapies. The cDNA arrays should allow a more objective grading system of tumors and offer the possibility to determine the prognosis of pre-malignant lesions. Nevertheless, there are a number of drawbacks that need to be overcome before this new technology may revolutionize the work of today’s pathologist. Besides the high costs of the equipment and the arrays themselves, traditional formalin-fixed material is unsuitable for expression profiling. There is a significant amount of non-neoplastic tissue in most tumors and the gene expression profile of these “normal” cells must be subtracted in order to obtain the expression fingerprint of the malignant cells. In addition, there is a considerable amount of heterogeneity within tumors so that the expression profile of one tumor sample may not be representative for other areas of the tumor. Thus, in the foreseeable future, the cDNA array technology will be particularly useful for an improved diagnostic approach to hematological neoplasias since these tumors are probably more homogenous and it is easier to obtain high quality RNA from leukemia and lymphoma cells than from solid tumors.

2.1 Gastrointestinal Cancer

2.1.1 Preoperative Diagnosis in Patients with Pancreatic Cancer

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Surgical resection with negative margins is the only potential chance of cure in patients with pancreatic or periampullary cancer. At the time of initial diagnosis, however, only a minority of patients present with resectable disease. Contraindications to resection are locally advanced T4-tumors (e.g. arterial infiltration, portal vein occlusion), distant metastases and peritoneal seeding. Beyond the mere diagnosis of the carcinoma preoperative diagnosis, therefore, has the goal to exclude technical or oncological irrespectability or to provide information leading to the initiation of neoadjuvant chemoradiation. In general, diagnostic measures must exclude liver metastases, peritoneal seeding and infiltration of the large blood vessels. An exception may be the isolated infiltration of the portal vein (without vein occlusion) which alone is no contraindication for resection. Modern CT-based and MRI-based diagnostic strategies are currently used in diagnosis and staging and have approximately the same diagnostic value. In contrast to CT, MRI has the advantage of also imaging the pancreatic and bile duct (MRCP). In doubtful cases, further examinations may be added. Endosonography, conventional angiography, ERCP and duplex sonography may provide further information regarding tumor resectability. The role of PET in excluding metastases is evolving but definitive data to define its value in preoperative staging are still lacking. The problem of all types of diagnostic measures is that accuracy in predicting resectability is in the range between 50 and 90%. Even with a combination of several diagnostic measures, at least 10% of the patients are found to be irresectable during subsequent laparotomy. The tumor marker CA 19-9 has an accuracy of about 80% in the diagnosis of pancreatic cancer per se. In many but not all patients the CA 19-9 level correlates with the overall tumor mass. A value of greater than 1000 U/l has been shown to predict irresectability with a relatively high accuracy.

Laparoscopy is used increasingly in the staging of several types of gastrointestinal cancers and may provide further information. It should be used in pancreatic cancer patients before neoadjuvant therapy (to exclude peritoneal seeding or liver metastases). Laparoscopy may also be used before laparotomy in patients with pancreatic cancer and no need for palliative surgery to prevent unnecessary laparotomy.

2.1.2 Epidemiology and Histopathological Classification of Pancreatic Carcinoma

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Carcinoma of the pancreas has markedly increased in incidence over the past several decades, and ranks as the fifth leading cause of cancer death in the United States. Despite the high mortality rate associated with pancreatic cancer, its etiology is poorly understood. Approximately 85–90% of carcinoma of the pancreas are ductal adenocarcinomas with its histological variants adenosquamous carcinoma, un-
differentiated carcinoma, mucinous noncystic carcinoma, signet ring cell carcinoma and mixed ductal-endocrine carcinoma. Carcinoma of the pancreas is commonly identified by the site of involvement within the pancreas and surgical approaches differ for masses in the head, body, tail, or uncinate process of the pancreas. The staging system for pancreatic exocrine cancer continues to evolve. The Union Internationale Contre le Cancer (UICC) has designated staging by TNM classification. A primary goal of a histological classification scheme is, in addition to staging and grading, assessing the prognosis of neoplasms. Cancer of the exocrine pancreas is rarely curable and has an overall survival rate of less than 4%. The highest cure rate occurs if the tumor is truly localized to the pancreas; however, this stage of disease accounts for fewer than 20% of cases. For those patients with localized disease and small cancers (< 2 centimeters) with no lymph node metastases and no extension beyond the „capsule“ of the pancreas, complete surgical resection can yield actuarial 5-year survival rates of 18% to 24%.

2.1.3 Pancreatic Cancer – Is Surgical Therapy the Best Therapeutic Option?

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The prognosis of patients with newly diagnosed pancreatic cancer is dismal in the majority of patients. Due to the lack of specific symptoms many of the patients present with locally advanced disease. In this group of patients the mean survival time is measured in months. For patients with limited disease, however, there is general agreement that surgical resection provides the only chance of cure. This implies that a R0-resection can be achieved. R1-resections do not prolong long term survival in pancreatic cancer patients. Due to major advances in operative technique and perioperative management the operative mortality in specialized centers is below 5%. Perioperative morbidity continues to decline. Perioperative morbidity and mortality is clearly related to the number of pancreas resections performed per year in the respective center. According to the local situation the classical Whipple operation has been modified in several aspects in the last years. In two thirds of the patients a pylorus preserving resection of the head of the pancreas is adequate providing improved recovery and less late complications after operation. Lymph node resection is now performed in most of the specialized centers in an extended form i.e. up to the right side of the upper mesenteric artery. Thereby a more accurate staging and hopefully a reduced local recurrence rate is achieved. Complete clearance of the superior mesenteric artery, however, should be avoided because of debilitating diarrhea. Total pancreatectomy instead of partial pancreatic resection does not result in an improvement of long term survival. Since the risk of the pancreatic-jejunostomy anastomosis could be substantially reduced and since 20% of totally pancreatectomized patients suffer from Brittle diabetes, the extent of pancreatic resection should be determined only by the local spread of the tumor. Vascular involvement has long been regarded as contraindication for surgical intervention in patients with pancreas carcinoma. Meanwhile resection of the portal or superior mesenteric vein can be performed without increasing the perioperative risk and will provide in a subgroup of patients the only chance for an R0 resection. Five year survival rate after complete resection of pancreas carcinoma reaches only 20-30 %.

Therefore, multimodal therapy is studied in many centers. At the moment neoadjuvant radiochemotherapy seems to be most promising.

2.1.4 Multimodality Treatment of Pancreatic Carcinoma

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The prognosis of pancreatic carcinoma is still dismal. Although resection rate and perioperative mortality could be reduced recently, an improvement of survival even using radical surgical approaches could not be achieved. Therefore, it seems evident that a multimodality approach is necessary and some studies using combined treatment options have already been published. In a prospective randomized trial an improvement of median survival from 11 to 23 month could be documented for adjuvant chemotherapy after R0-resection of pancreatic head carcinoma. However, 5-year survival rates did not differ. Also in the largest prospective randomized trial published so far an increase of survival after adjuvant chemotherapy (5-FU, folinic acid) was seen.

For adjuvant radiochemotherapy in the same trial no benefit was reported compared to the control group. This result is in accordance with a recent study (EORTC 1999), however, it is in contrast to an older trial (GITSG 1985). Currently, new protocols using gemcitabine as radiosensitizer are under investigation. Radiotherapy alone presumably has no positive effect.

The approach currently most intensively discussed is neoadjuvant radiochemotherapy. Conclusive data from prospective randomized trials however are still lacking. Only proof of principle results showing low morbidity are available.

In the palliative treatment of pancreatic cancer Gemcitabine monotherapy has emerged as standard after an improvement of survival could be shown. Currently combination of Gemcitabine is investigated.

In summary adjuvant chemotherapy seems to have an a beneficial effect on median survival. Neoadjuvant radiochemotherapy seems a promising concept however survival data to support this approach are still awaited.

2.1.5 Systemic Treatment of Advanced Pancreatic Cancer

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Pancreatic cancer remains one of the major unsolved health issues with an incidence of 10 per 100.000 per year and the poorest survival among the common malignancies. It is estimated that in Europe around 50.000 patients are diagnosed with this disease each year with a similar death rate due to the fact that the vast majority of diagnoses is made in an advanced stage. The median survival is 8–12 months for patients with localized disease and 3–6 months with metastatic spread at initial presentation. For localized stages neoadjuvant combined chemo radiotherapy approaches are being increasingly investigated in order to improve on the rate of complete surgical resection, which remains to be the only chance for cure in this dismal disease. This discussion will focus on the advances of systemic chemotherapy in the treatment of advanced disease, although there is no doubt that optimal management of these patients is accomplished within a multidisciplinary setting.

In general, single agent chemotherapy has been the mainstay of treatment in patients with advanced disease, with objective response rates rarely exceeding 10%. However, traditionally used endpoints such as bi-dimensional tumor measurement to assess the efficacy of systemic chemotherapy have been difficult to apply in pancreatic cancer be-
cause imaging studies may be confounded by a strong desmoplastic reaction of the pancreatic tissue and by the difficulty to exactly delineate malignant tissue borders. For these reasons parameters considered to reflect a 'clinical benefit response rate' with evaluation of improvement of quality of life, of performance status and prolongation of overall survival have been used in more recent trials. Only two drugs, namely 5-fluorouracil and gemcitabine have consistently been associated with a survival of > 5 months. In a prospective trial newly diagnosed patients with advanced pancreatic cancer were randomized to receive either gemcitabine (1000 mg/m² weekly) or 5-FU (600 mg/m² weekly; J Clin Oncol 1997;15:2403), 24% in the gemcitabine arm versus 5% (5-FU) experienced a clinical benefit, defined as improvement of at least one of the following factors without deterioration of any other factor: pain, performance status, weight. Overall survival was 5.6 (gemcitabine) versus 4.4 months. The results of this study established gemcitabine as the accepted first line treatment for advanced pancreatic cancer. During the last five years the moderate but superior activity of gemcitabine as a single agent has been confirmed. The emergence of a variety of effective classical chemotherapeutic agents as well as new agents such as EGFR antagonists for the treatment of gastrointestinal cancer has raised enthusiasm for improvement of therapy in pancreatic cancer as well. Several phase II studies have combined gemcitabine with newer agents such as irinotecan, oxaliplatin, docetaxel, paclitaxel and pemetrexed. As a trend the response rates and one-year survival have headed towards 30%, a moderate but nevertheless distinct progress. Several phase III studies are currently comparing standard gemcitabine versus any of those combinations.

In summary at present single agent gemcitabine remains the standard of care for the treatment of advanced unresectable pancreatic cancer. In order to learn whether the addition of any of the new agents may further improve the therapeutic efficacy, enrollment of patients in well-designed therapeutic trials is mandatory.

2.1.6 Molecular Pathology of Colorectal Carcinomas

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The establishment and progression of cancer is a multi-step process, involving both genetic and environmental events. The molecular mechanisms underlying carcinogenesis and cancer progression can now be evaluated using novel laboratory techniques, such as cDNA arrays, and the results may provide essential information for designing tools for early detection of cancer, for intervention and monitoring strategies.

In colorectal cancer, a clearly heterogeneous disease, the definition of a single molecular pathway responsible for tumor initiation and progression is not feasible. In fact, there are many suggestions as to the nature of the molecular hallmarks of CRC. Firstly, specific genetic aberrations have been shown to correlate to the histopathological sequence of normal colon > adenoma > carcinoma. An accumulation of activating mutations of oncogenes (e.g. k-ras) together with inactivating mutations or loss of tumor-suppressor (e.g. APC, p53) or DNA mismatch repair (e.g. MLH-1, MSH-2) genes has since then dominated the view of molecular pathology in sporadic CRC. However, other molecular aberrations have been implicated in CRC. In particular, inactivation of specific cellular processes (DNA repair, cell cycle control) by methylation of involved genes (e.g. MLH1, p16) appear to be involved in subsets of CRC. Moreover, the concept of microsatellite instability (MSI), has gained more attention in sporadic CRC where up to 15% of cases show MSI. Finally, for the inherited syndromes of hereditary nonpolyposis colorectal cancer (HNPCC), accounting for about 5% of CRC cases, and familial adenomatous polyposis (FAP) germ line mutations of DNA mismatch repair and the APC genes, respectively, have been defined.

Clearly, the heterogeneous nature of CRC is reflected by involvement of numerous, interacting molecular pathways. Stratification of CRC patients according to the histopathological and molecular 'fingerprint' of the tumor tissue may be essential for definition of specific prognostic groups and/or for selection of patients for specific anticancer therapies.

2.1.7 The Role of CT and MRI in Colorectal Cancer Imaging

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Colorectal cancer is the second most common form of cancer in developed countries. Local spread and lymph node status heavily influences the therapeutic strategy in the initial onset of tumor and follow-up situation. For planning of surgical and radiation therapy, ex-act staging is mandatory. The role of imaging is to provide information regarding tumor location, size, configuration, and degree of local infiltration. The entity of the large bowel has to be visualized in order to exclude synchronous lesions. Assessment of transmural tumor spread demands clear differentiation of the colorectal wall layers, the perirectal fat tissue and adjacent organs and vessel structures. The role of different imaging modalities in the diagnostic work-up of patients with colorectal cancer is still discussed controversially. With Endorectal ultrasound (EUS) high resolution depiction of the bowel wall layers and adjacent lymph nodes is possible. Accuracy for T-Staging has been found to range from 76–96% for T1–T3 stage. MRI using endorectal coils (EMRI) combines high spatial resolution imaging with the excellent soft tissue contrast inherent to the method. The reported accuracy of approx. 80% in T-and N-Staging turned out to be similar to EUS. However, endoluminal coil application bears the same drawbacks of the method compared with EUS. Recent technical advances have overcome many limitations of MRI regarding limitations of spatial resolution and signal exploitation. Combining a phased-array coil with high-gradient scanner systems, excellent image quality can be obtained without use of dedicated endoluminal instrumentation. Multiplanar imaging makes optimal slice orientation according to the bowel course possible. With sagittal and coronal views the distinction between bowel wall borders and adjacent organs is easier. Partial volume effects can be minimized and the anatomic topography becomes much clearer for surgical planning. Compared with endoluminal examinations like EUS or EMRI the entire abdomen can be scanned for tumor spread, lymph node involvement and distant metastases. Whereas accuracy is limited in T1/T2-situation, PPV/NPV is high for T3 stage with 81/93%, respectively. T4 stage commonly can be assessed with certainty looking at signal alterations in adjacent organs and the fat layer criterion. Detection of lymph node is hampered by limited correlation between lymph node size and presence of tumor involvement. Using high-resolution sequences 3mm sized lymph nodes can be depicted. Rounded shape, central necrosis and conglomerate distribution are signs of malignancy but reactive changes can mimic these findings. Specific lymphophototropic contrast agent like USPIO are investigated in current studies and are promising in differentiating benign from malignant lymph nodes.

With introduction of the Multislice technique CT has gained rising importance in oncology imaging compared with MRI. Earlier studies have found quite disappointing accuracy for colorectal tumors being examined with single-slice CT ranging between 48% and 77%. Multislice CT (MSCT) however provides both, coverage of a large field-
of-view with excellent spatial resolution. Combining rectal filling with 1mm-collimation data acquisition, a diagnostic accuracy of 96% has been reported for rectosigmoid cancer recently. Although soft tissue contrast always is minor to MRI, high-quality multiplanar imaging with isotropic voxels now is possible with MSCT either. Moreover, virtual endoscopy and sophisticated 3D-presentations can be performed using the axial CT source data set.

2.1.8 Colorectal Carcinoma: Endoscopic Diagnostic Procedures and Current Protocols of Local Therapy

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The incidence of colorectal cancer is increasing worldwide. In general, 1 out of 20 individuals will be affected by this disease, so that in the European Community approximately 200,000 cases per year are diagnosed. The post-surgical survival is directly related to disease stage at the time of diagnosis. Screening detects these cancers at earlier stages than those identified when symptoms develop. Colonoscopic screening in the ‘average-risk individuals’ is estimated to prevent 75% of colorectal cancer compared with 34% for sigmoidoscopy and 16% for occult blood testing.

In our clinical routine, we evaluate every rectal malignancy by endorectal sonography (7.5 MHz) to evaluate the depth of wall infiltration or penetration as well as the perirectal tissue including lymph nodes. This technique has an overall diagnostic accuracy of approximately 90% for rectal cancer. In order to improve the long-term results and to individualize therapeutic approaches, an early and precise staging of colorectal carcinomas is mandatory.

Radical resection is the surgical principle in the treatment of colorectal carcinoma. On the other hand, recent improvements in surgical techniques have allowed more patients with rectal cancer to undergo sphincter sparing operations.

Under a curative intention, local excision of distal rectal tumors (located 2 to 14 cm from the anal verge) can be performed by transanal endoscopic microsurgery (TEM). Compared with conventional transanal resection, TEM provides superior exposure of tumors located higher up in the rectum. In our department, patients for transanal excision include T1 rectal carcinomas at all differentiation levels. Since the risk of lymphatic metastasis for low and moderately differentiated T2 rectal carcinomas reaches 6% and therefore exceeds the risk of transabdominal surgery, we only resect highly differentiated T2 rectal carcinomas transanally. Due to reduced resection margins from the cancer with TEM or conventional transanal excision compared to transabdominal resections, the local recurrence rate reaches 11 to 14% and is slightly higher than after an anterior or abdominoperineal approach.

In conclusion, the greater precision of resection combined with a low morbidity makes transanal excisions a reliable alternative for a selected group of patients with low risk rectal carcinomas. In the future, the question has to be answered whether (neo-) adjuvant therapies can further improve the results of local excisions of rectal carcinoma in selected patients.

2.1.9 Did Standard Surgical Practice Change in Colorectal Surgery?

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Although recently colorectal surgery experiences a more individualized and multimodal therapy surgical procedures still rely on oncological principles like the ‘no-touch’ isolation technique with vascular and luminal exclusion of the tumor segment and ‘en-block’ resection of the respective lymph nodes and -vessels. These principles form the basis of the surgical standards, however, most of them are not evidence-based. Nevertheless, it is assumed that removal of the lymphatics may be beneficial since ~40% of them are infiltrated by malignant cells at the time of diagnosis. Since they run with the blood vessels the extent of the resection of a colonic tumor is anatomically defined: a tumor of the coecum or C ascendens is treated by a right hemicolectomy with central division of the ileocolic and right colic arteries; a tumor of the left colon by a left hemicolectomy with division of the left colic artery close to its origin at the aorta. Controversy still exists as to whether low or high tie is the right choice in the case of a sigmoidal carcinoma. Total mesorectal excision (TME) for the middle and lower third of the rectum or partial mesorectal excision (PME) for the upper third has become the standard operation in rectal carcinoma. Performing TME local recurrence rates from up to 38% could be lowered below 10% even in low volume hospitals after thorough surgical instruction. Today, low rectal carcinoma is treated by sphincter sparing procedures in almost 95%, thus reserving proctectomy for very deep, huge or sphincter infiltrating carcinomas. Reconstruction after removal of the lower rectum (deep anterior or intersphincteric resection) should include some type of pouch formation (mostly J-pouch) since short- and even long term quality of life is superior to that after straight anal anastomosis. Laparoscopic surgery has been extended to colorectal surgery, firstly for benign, later also for malignant disease. Initial enthusiasm was hampered by reports about ‘port-site’ metastases. Furthermore, the duration of the operations, the beneficial effect (if any) and the possible violation of oncological surgical principles were criticized. Improvement of the minimal invasive technique and appreciation of the long learning curve have led to similar results as open surgery with respect to number of lymph nodes removed, resection margins, complication rates and mortality. Hospital stay was shorter and postoperative pain seemed to be less in laparoscopic surgery. So far, results with respect to 5-year survival or disease free survival are very scarce. Therefore, laparoscopic resection of colorectal carcinomas must be limited to centers involved in prospective randomized trials which are being conducted.

In summary, oncological principles and surgical standards in the treatment of colorectal carcinomas have not changed, but surgical approach has been extended to laparoscopic surgery. It is feasible, but recommendations may be given not until more definite results from ongoing randomized trials are available.

2.1.10 Colorectal Cancer: Results of Multimodal Treatment

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The prognosis of a patient with colorectal cancer depends on the optimized surgical therapy. Total removal of the tumor (= Ro-resection) allows to cure the disease, only.
In rectal cancer adjuvant chemo/radiotherapy reduces in stage II and III the local recurrence rate about 50%. Actually, in these stages the adjuvant therapy with 5-FU in combination with radiotherapy represents the standard strategy.

New substances like capectabin will be evaluated in controlled trials. A new strategy with neoadjuvant high dose radiotherapy can reduce the local recurrence in some subgroups. The short time radiation with 5 × 5 Gy and subsequent tumor resection with total mesorectal excision in tumors localized in the middle of the rectum and in stage III improves the local recurrence rate.

In tumors with stage I or II and/or with deep or high localization in the rectum this therapy has a little effect only. In advanced tumors the radiotherapy (45 Gy) combined with a 5-FU chemotheraphy shows a downstaging in 63%. A complete remission was seen in 5%.

In colon cancer with stage III the adjuvant chemotherapy with 5-FU/FA bolus therapy for 6 month is the recommended treatment. New concepts (Capecitabin, Irinotecan, Oxaliplatin) has been evaluated in some trials. The follow-up is not yet finished. Adjuvant therapy in stage-II colon cancer should be performed only in controlled trials, because the published data are controversial.

2.1.11 Adjuvant Radiotherapy of Rectal Cancer

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A new strategy is urgently needed because still up to 30% of patients develop recurrent disease after curative surgical resection of rectal cancer. At present studies are underway to evaluate the value of some new strategies. Nevertheless, the pelvic radiotherapy per se is nowadays undisputed and accepted in all trials concerning locally advanced rectal cancer. Combining innovative radiation techniques with highly promising new cytotoxic agents like Capecitabin, Irinotecan, Topotecan, and Oxaliplatin could give a new and promising impulse to improve the outcome of the rectal carcinoma.

The National Institute of Health Consensus Development Conference recommended the administration of radiation therapy in combination with fluorouracil (5-FU) chemotherapy, as it was shown that this strategy improves local control and overall survival in patients with stage II and III rectal carcinoma. This recommendation was based on two trials: The Gastrointestinal Tumor Study Group (GITSG) in 1985 and the North Central Cancer Treatment Group (NCCTG) in 1991. Since this time many attempts aimed to improve the efficiency of chemo-radiotherapy by administering semustine, nitrosourea, levamisole, and leucovorin. Most of them failed to exceed the standard therapy. Additionally, the 5-FU administration schedule was modulated and altered schemes of radiotherapy were analyzed, including modifications of fractionation and evaluation of pre- or postoperative radiotherapy.

The major indications for radiotherapy are: the reduction of local recurrences in mobile rectal cancer, downstaging of the tumor in primary irresectable tumors and down sizing of low-lying tumors in attempts to more frequently perform a sphincter-saving procedure. Both preoperative and postoperative radiotherapy reduce the number of recurrences and improve survival, but, obviously, only preoperative radiotherapy is a suitable option for downstaging or downsizing.

The radiotherapy of the rectal carcinoma is well-tolerated and can be refined by using new technologies like IMRT (intensity modulated radiotherapy), conformal radiotherapy or IORT (intraoperative radiotherapy). Conventional radiation techniques include delivery to multiple fields, computerized treatment planning, and customized blocking rather than the use of simple anterior–posterior fields. These techniques allow the delivery of higher doses while sparing the surrounding normal tissues, such as the small intestine. The clinical target volume include the sacrum, the presacral space, the posterior walls of the bladder, and the regional lymph nodes extending to the common iliac artery. Postoperatively, a total dose of 50.4 Gy is delivered in 1.8 Gy daily fractions over a period of approximately six weeks.

In order to fathom out the patterns of care, we conducted a retrospective analysis of 350 rectal carcinoma patients (8/93–12/2000), including tumor data, strategy, survival, treatment and local control. 155 (44%) patients were treated postoperatively with adjuvant, 44 (13%) preoperatively with a neoadjuvant regime (radiotherapy and fluorouracil) and 78 (22%) with a tumor relapse. Median survival of patients with tumor relapse is 15.2 months. Median survival for adjuvant therapy is 28.9 months and for neoadjuvant therapy 21.3 months (other 12.1 months).

In conclusion, promising new attempts were made to improve the outcome of rectal cancer patients, considering local control, survival and quality of life. Radiotherapy will be part of the multimodal concept, but at the current time neither the succeeding-agent of 5-FU can be determined nor the question can be answered whether pre- or postoperative radiotherapy is more efficient.

2.2 Oncology in the Elderly

2.2.1 Geriatric Oncology: 1. Basic Data and Risk Factors; 2. Assessment and Risk Stratification

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According to demographic changes frequency of cancer in the old aged will increase and therefore cancer will become the No. 1 cause in lethality and mortality within the next decade [1,2]. In contrast to its demographic and economic relevance geriatric oncology neither plays a significant role in geriatrics, nor in oncology. This paradoxical discrepancy may be due to some typical reasons. So we know that the situation of the old cancer patient is frequently accompanied by several problems and misunderstandings as well. Thus, elderly cancer patients are often inadequately diagnosed and treated at all. This is because of a wide spread prejudice that age itself is a risk factor and associated with higher toxicity and low therapeutic outcome. In contrast, several meta-analyses and few prospective studies have shown that clinical results will not differ from younger individuals when taking into account the specific age related modified organ functions especially of renal and hepatic parameters. Furthermore, several age related compromising changes in motor function, in functional status and social conditions are framing the context of treatment for malignant diseases in elderly patient and do also play a significant role for the prognosis and treatment outcome. Validated geriatric assessment instruments have been developed to identify these specific factors, but the assessment should be followed by systematic interventions and effective symptom control. Supporting patients in their activities of daily living (ADL) and in their motor and cognitive functions is clearly related to success of anticancer treatment in elderly patients. The psychosocial status of elderly cancer patients has a significant influence together with patient’s wish of being treated on the base of the individual prognosis and the quality of life during the treatment process. With respect to the overall importance of ‘Geriatric oncology
topics’ more research will hopefully be directed into this field in the future. Interdisciplinary training and common understanding is important for diagnosis, therapeutic decision and achieving therapy goals in elderly cancer patients. However, the cooperation between oncology and geriatrics in Germany is still not sufficiently developed. Thus, a transfer of knowledge between geriatric medicine and clinical hematology/oncology is urgently needed and was previously proven to be highly effective [3]. The present situation has formed the groundwork to initiate an interdisciplinary working group on ‘Geriatric Oncology’ which has been established by the ‘German Society of Hematology and Oncology’ (DGHO) and the ‘German Society for Geriatric medicine’ (DGG) in 1999.

2.2.2 High-Dose Chemotherapy and Autologous Stem Cell Transplantation in Elderly Patients: Is there an Upper Age Limit?

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Many hematological malignancies increase in incidence with age such as AML, MDS, NHL, and multiple myeloma. In older as compared to younger patients (pts), the disease and therapeutic response can be intrinsically different. Elderly pts are also more difficult to treat due to concomitant medical problems such as co-morbidity, diminished organ functions, altered drug metabolism, and irregular drug clearance rates [1–5]. Thus, potential risk factors must be carefully considered when evaluating treatment options for older pts. Although high-dose therapy with ASCT is a widely used method of dose intensification in pts with hematological and non-hematological malignancies [6–8], pts > 60 are generally excluded due to an anticipated increased risk of regimen-related toxicities and mortality with age. Since in neoplastic disease the median age is often well > 60, a large proportion of pts are excluded as candidates for ASCT exclusively for reasons of age. Nevertheless, the rise in age-related incidence justifies reevaluation of current therapies, including high-dose chemotherapy and ASCT for elderly pts. Recently, several investigators have raised the upper age limit for ASCT because of encouraging results [1–4]. These have in part been obtained because of changes in transplantation practice, including use of cytokines, use of peripheral blood stem cells (PBSC) instead of bone marrow, less toxic conditioning regimens, and prolonged post-transplant monitoring and antibiotic prophylaxis. These changes in transplantation standards have allowed pts of more advanced age to be considered on an individual basis and have reduced the toxicity of ASCT. In this area of growing interest on the use of high-dose therapy and ASCT in patients > 60 we will present data on the toxicity of ASCT. In our institution, the upper age limit for ASCT has at present increased from 60 to 70 years. Since pts eligible for high-dose therapy with ASCT still represent a selected group, namely with good performance status and without general organ impairment, future clinical trials are warranted to identify those pts likely to benefit most from this approach.


2.2.3 Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML) – a Biological Continuum?


AML is a rare disease (3–4 cases/100 000/year) mostly occurring in patients above 55–60 years [1]. Several or probably even numerous biological steps including myelodysplasia may precede this disease, which has an incidence of > 20/100 000/year in patients > 70 years. Thus in individuals over 70 years, MDS may represent the most frequent hematological disorder [2]. In contrast, in patients below 55–60 years, the incidence of myelodysplasia and of AML preceded or accompanied by dysplastic morphologic features is much lower. Recently, an association between certain cytogenetic abnormalities, such as deletions or monosomy of chromosomes 5 and 7, and/or complex cytogenetic changes, have been described for both high-risk MDS and AML of the elderly [3]. Another unifying feature of MDS with a significant blast expansion and of AML is DNA methylation and thus silencing of genes. Until recently, the (arbitrary) cut-offs of 21–30% bone marrow blasts were used by the FAB classification to define the MDS in transformation to acute myeloid leukemia (RAEB-t). To take into account the biological continuum between MDS with blast expansion and overt leukemia, the WHO has proposed to lower the cut-off levels for definition of AML from > 30 to > 20% bone marrow blasts [4]. This also reflects the fact that treatment options may be quite similar in this patient subgroup. However, treatment decisions are not only based on blast percentages and cytogenetics [5] but on parameters that are sometimes difficult or complex to capture, i.e. biological age, co-morbidity and overall performance status of patients [6]. Thus, in patients below the biological age of 55–65 years, induction chemotherapy followed by consolidation (if possible autografting which has the highest cure rate) is the aim of treatment. In patients
above this biological age and in whom allogeneic transplantation does not appear as a reasonable option, more adequate, novel treatment approaches need to be developed [7]. In the past, low-dose chemotherapy (sometimes with the rationale of differentiation-induction, e.g. with low-dose Ara-C), has been employed. However, since its main effect is not differentiation but cytotoxicity, inhibition of angiogenesis (thalidomide), of DNA methylation (azacucurules such as 5-azacytidine and decitabine) and of histone deacetylation (sodium phenybutyrate, depsipeptide) offer new and possibly more successful options. An upfront assessment of the patients to document the key parameters (performance status, co-morbidity etc.) accounting for treatment decisions, either induction and transplantation, or treatment with novel agents, or best supportive care only, appears important, as well as analyses of the time spent in the hospital [8] and of quality of life.


2.2.4 Obligation to Treat? Ethical Aspects of Haemat-Oncology

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One of the most urgent problems of cancer treatment is the problem of coping with incurability and termination. Advances of oncology serve clearly the interests of the sick in their further life with the disease. As long as these problems stay unsettled we find a vacuum in the background. If medicine based on its responsibility for an adequate care does not try to solve these problems this field becomes occupied by health economy and politics. Often the goal of a cancer treatment fails to guarantee living related to the irreversible progress of the illness. All the stronger becomes the physician’s duty to resign further curative and burdening treatment. This duty must notice this turning point, i.e. shift its efforts from curing to palliation in these phases.

Ethical considerations have to show:
1. Dying also belongs to one’s life and requires adequate interventions from the caregivers. Quality of life is part of the patients’ interests. Caregivers are obliged to protect it.
2. Which measures are part of the physician’s duty? What can medicine do when it can not cure the disease? To know these details of a treatment plan may transgress the every-day practice of medicine, but the duty to support these irreversibly ill people and to ask colleagues for counseling them is indispensable.
3. How and why can the traditional ethos of prolonging life be changed to a morality of life support — or in terms of moral psychology: to an ethos of assistance in developing life?
4. How can withdrawal, withholding, and reduction of treatment be distinguished from measures of active euthanasia?

2.2.5 Complementary Cancer Treatment in Older Patients

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Complementary and alternative medicine (CAM) is increasingly popular in Germany and the USA. More than 50% of European cancer patients are using CAM. Most frequently used are mistletoe preparations (60% of cancer patients using CAM). The typical CAM user is young, female and has a strong internal health locus of control and an active coping strategy. There is, however, also a need for information about CAM in older patients. According to a survey in 2000 about 40% of cancer patients > 60 years of the Medical Department of Freiburg University Hospital indicated an interest in a consultation about CAM.

For mistletoe preparations, thymic peptides and proteolytic enzymes there are interesting clinical and preclinical data about antitumoral and immunomodulating effects. An effect on the survival time of cancer patients however could not yet convincingly be proved. Recently the effect of a mistletoe preparation on the quality of life (QoL) of patients during chemotherapy with colorectal carcinoma and breast cancer could be demonstrated in two controlled randomized studies. QoL plays an important role in the management of older cancer patients. Depression or sleeping disorders are frequent problems which deteriorate the QoL. Therefore a symptomatic treatment with e.g. standardized preparations of St. John’s Worth for mild and moderate depression or valerian for sleeping disorders may be helpful within the supportive care. The effectivity and good tolerability of these medications has been demonstrated within controlled studies. Possible drug interactions of St John’s Worth due to increased induction of cytochrome P450 however have to be taken into account. Apart from medications physical exercise, adequate nutrition and personal attention play an important role also in the supportive care of older patients

2.2.6 Latent Nutrition Deficits and Vitamin Deficiencies

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The group of senior citizens is very variable, which explains the very different findings concerning health status of old people. Differences can be found at the various age-groups, but also in examinations for aged persons living at home respectively in old peoples nursing homes. Whereas overweight and diseases related to this cause are major problems of the middle aged groups, malnutrition and undernutrition gain importance in age. Looking at it in a simple way, malnutrition is the result of a negative energy - respectively nutrient balance and consequently insufficient nutritional intake. The nutritional intake and the nutritional status in age are influenced by physiological changes caused by age (decrease of appetite and thirst, reduction of taste and smell sense, a changed regulation of hunger and satiation, difficulties in chewing caused by loss of teeth), age related alterations of the gastrointestinal tract and in the body composition (loss of fat free mass), the nutritional behavior with unbalanced nutrition and lack of adaptation to a needed higher nutrient density based on lower energy requirements, physical disabilities (disfunctions of mobility, disabilities of nutrient intake, complaints in chewing and swallowing), disease and drug effects (maldigestion and malabsorption, increased loss of nutrients, increased requirements), cerebral and psy-
chological disturbances (forgetfulness, dementia, depression) and socio-economic factors (loneliness, financial problems, domicile situation, loss of partner). Because insufficient nutrition leads to loss of function and therewith further development of diseases, an appropriate nutrition is considered as a essential factor for an improved and longer life, good health and quality of life. In a consensus meeting in 2001 to ‘nutrition and aging’ the most critical micronutrients in the nutrition of seniors are namely Vit B₁₂, folic acid and Vit D in combination with adequate calcium intake. The protein bond Vit B₁₂ of the nutrition is absorbed in the stomach with hydrochloric acid and peptic pH-dependent on r-proteine respective in lesser degree on intrinsic factor. In upper small intestine cobalamin under the influence of pankreastrypsin is released from its linkage, bound at intrinsic factor and reabsorbed in terminal ileum by aid of specific receptors. With increasing age the named premises for an optimal Vit B₁₂ resorption are impaired, because the basal and histamin stimulated hydrochloric acid secretion of the stomach decreases. An additional problem is the common existing chronic gastritis with sub- and anacidity and diminished intrinsic factor production. Sub- and anacidity lead to an inferior utilization of the protein bound Vit B₁₂, the in case of sub- and anacidity regularly detectable bacterial colonization of the stomach induces consumption of Vit B₁₂ and also the bacterial synthesis of substances, who compete with Vit B₁₂ for the receptors in the ileum-mucosa. Also antacid decrease dose-related the Vit B₁₂ resorption, just as the oral diabetic drug metformin does. With reduced acid secretion also the folic acid secretion may be reduced. The deficiency of Vit D and calcium is the consequence of the diminished Vit D synthesis in the skin and of an insufficient intake and resorption of Vit D and calcium. High attention must be paid particularly to the intake of Vit C (smokers), Vit E, iron, zinc and selenium. The intake of Vit A, retinoids, Vit K, Vit B₁ (alcohol consumption), Vit B₂ and Vit B₆ is of medium priority.

2.3 Innovative Treatment Modalities

2.3.1 Cancer Gene Therapy: Hard Lessons and New Courses

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For most patients with advanced or multifocal malignant tumors treatment options are limited resulting in a poor prognosis. Therefore, the development of novel therapeutic strategies such as immune therapy and gene therapy is highly required. Gene therapy for the treatment of cancer was initiated with high levels of optimism and enthusiasm. Recently, this perception has had to be tempered by the realization that efficiency and accuracy of gene delivery remain the most significant barriers to its success. So far, there has been a disappointing inability to reach target cells with sufficient efficacy to generate high enough levels of direct killing resulting in the need for bystander effects for any potential strategy to be convincing. Clinical advance, therefore, will come from cooperation with more established approaches such as chemotherapy and immunotherapy. Until now, a variety of specific and unspecific immunomodulatory strategies have been applied clinical trials with some promising results. The molecular characterization of tumor associated tumor antigens such as α-fetoprotein (AFP) and the increased understanding of the immunological pathways involved in tumor immunity have paved the way for the design of promising gene-based cellular cancer immune vaccines. The most important and widely used immunotherapeutic approaches consist of whole-cell vaccines, dendritic cell-based immunotherapy, and peptide vaccines. Clinical trials have, in general, demonstrated the safety of such strategies. Recently, exciting new immunological techniques and tools have been developed which allow to characterize antigen specific T cells at a single-cell level. In future, specific tumor rejection antigens have to be identified using new approaches such as reverse immunology which can be targeted therapeutically. A better quality control of the different immunotherapeutic approaches is mandatory if used in patients and the different therapeutic modalities need to be compared directly. To understand the limitations and exploit the full potential of the different approaches it is essential to get a thorough understanding of the clinical situations in which gene and immunotherapy will be used. This will enable to find the appropriate clinical niche in which its abilities will be optimal useful.

2.3.2 Adoptive T Cell Transfer

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The concept of adoptive cellular therapy is based on the observations that tumors are immunogenic and that transferred T cells can recognize and eliminate tumor cells. According to the immune-surveillance hypothesis, tumors express neo-antigens resulting from genetic instability of tumor cells and generally induce an immune response against those foreign, or non-self, tumor antigens. The development of tumors in the face of circulating lymphocytes was thought to be the result of various immune escape mechanisms that tumor cells employ to avoid elimination by the immune system. The observation that tumor specific CTL in melanoma patients are directed against normal melanocyte differentiation antigens led to a paradigm shift linking tumor immunology to autoimmunity in that most tumor antigens are self antigens and that mechanisms of tumor tolerance induction resemble those to avoid autoimmunity. In general, tumor tolerance can result from failure of the immune system to recognize the tumor (ignorance), or from active processes leading to tumor specific anergy or clonal deletion of tumor reactive cells. Stimulation with antigen loaded dendritic cells (DC) can prime naive T cells and break T cell tolerance in vitro and in vivo. For in vivo priming, antigen loaded DC can be applied as a vaccine. Alternatively, T cells can be primed with autologous DC in vitro and be re-transfused after expansion. The expansion of polyclonal and antigen specific T cells to numbers necessary for adoptive transfer has been facilitated by a recently developed method. Whether this method can be applied to expand tumor antigen specific T cells is currently under investigation.

The most powerful form of adoptive T cell transfer known today, however, is the transfusion of allogeneic T cells, or donor lymphocyte infusions (DLI), which has been particularly effective for the treatment of relapsed CML. The clinical benefit of polyclonal DLI for patients with acute leukemia or lymphoma is much lower, due to a lower response rate and a high risk of graft versus host disease. The transfer of tumor antigen specific donor T cells instead of polyclonal DLI, i.e. a potentially highly effective, well tolerable and specific immunotherapy would thus be a desirable alternative. Current research is focused on the generation of tumor antigen specific donor T cells in patients with AML or NHL.
Anti-angiogenic therapy is one of the most promising new strategies to inhibit malignant tumor growth and formation of metastases. Malignant tumors are not primarily integrated in the existing blood vessel system so that nutrient supply is initially acquired through diffusion from surrounding cells. Above a few mm in diameter this supply becomes limited, thus a connection to the vessel system is essential for growth and spread. In malignant tumors the development and spread of new capillaries is directed and regulated by a complex network, mainly by pro- (e.g. VEGF) and anti- (e.g. endostatin) angiogenic factors. This constitutes, that the physiological balance of these factors is disturbed in malignancies; its termed the angiogenic switch. The increasing knowledge on the mechanisms of tumor angiogenesis resulted in a large number of compounds with different targets. Recently, some of these compounds have entered clinical trials and can now be grouped in 1. Receptor tyrosine kinase inhibitors 2. Receptor antibodies 3. Antibodies 4. Physiologic inhibitors 5. Integrin inhibitors 6. Matrix metalloproteinase inhibitors and 7. Compounds with unknown mechanism. Benefits like the lack of drug resistance, complete remissions, independence from tumor entities, less or missing toxicity and long lasting efficacy were anticipated from animal studies. Until today, these findings could not be reproduced in man. Best responses observed are mainly stable diseases up to 15 month. A variety of mild side effects as well as non responder are described in preliminary publications. Furthermore, it turns out that some tumor entities (e.g. colorectal cancer, renal cell carcinoma and leukemia) respond better than others, influencing the design of future phase II/III trials. We learned from the actual clinical trials with antiangiogenic agents, that there might exist an angiogenic phenotype causing non responder, that surrogate markers (like soluble VEGF, decMRI) are necessary to detect biological active doses that might be below the MTD and that further understanding of the process of tumor angiogenesis is needed to optimize its use in humans. Therefore, future investigations concentrate on combination therapies, development of new surrogate marker and detection of new antiangiogenic targets.

2.3.4 Immunotherapeutic Strategies for Hepatocellular Carcinoma: Induction of Tumor Necrosis – an Adjuvant Concept for Immunotherapy of HCC?

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For most of the patients with advanced or multifocal hepatocellular carcinoma (HCC) options of treatment are limited resulting in a very poor prognosis. Therefore, the development of novel therapeutic strategies is highly required of which immunotherapeutic approaches may play a dominant role.

Until now, a variety of specific and unspecific immunostimulatory strategies against HCC have been applied in preclinical mouse models with some promising results. The molecular characterization of HCC-associated tumor antigens such as the alpha-fetoprotein (AFP) and the increased understanding of the immunological pathways involved in tumor immunity have paved the way for the design of promising gene-based cellular cancer vaccines. Clinical trials have, in general, demonstrated the safety of such strategies. In addition, several local ablation methods have been developed as minimally invasive strategies for the treatment of HCC. Reduction of the HCC burden by palliative local ablative approaches might be important for a consecutive success of adjuvant immunotherapies aiming at the deceleration or even prevention of occurrence of metastases or recurrent tumor growth. Furthermore, the induction of tumor cell injury and tumor cell death using such local procedures most likely yields in cell necrosis rather than apoptosis. As a result endogeneous activating substances may be released that can function as natural adjuvants to stimulate a primary antitumoral immune response. Therefore, the combination of immunotherapeutic approaches with local tumor ablation may act synergistically against HCC and in future, the young and promising scientific field of reverse immunology may reveal new HCC specific tumor rejection antigens, which can be targeted therapeutically, and thereby extend a successful combination of immunotherapeutic approaches against HCC.

2.3.5 Targeting Telomerase: A Universal Strategy to Combat Cancer?

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A major difference between normal and malignant cells is the ability of cancer cells to multiply in an unrestricted and unguided fashion [1]. It is now clear that the mechanism that confers immortality on cells in most types of cancer is related to the capability of maintaining their telomeres. Telomeres are specialized structures at the ends of chromosomes which are composed of TTAGGG repeats and associated proteins [2]. They are essential genetic elements and their major function is to provide stability and integrity at the ends of chromosomes. In normal somatic cells, these sequences are known to be gradually lost through successive cell divisions which ultimately leads to replicative senescence. In contrast, immortalized tumor cell lines and 80–90% of primary tumors counteract telomere erosion by activation of the reverse transcriptase telomerase which results in unlimited growth potential [3]. Moreover, telomerase activation appears to be one of the key events required for malignant transformation of normal cells.

With the cancer cell reliant on telomerase for its survival, telomerase represents a very attractive mechanism-based target for the development of new cancer therapeutics. Proof of principle was demonstrated using a genetic approach with a dominant-negative mutant of hTERT, which is the catalytic component of telomerase. By retroviral infection in several established tumor-cell lines and in xenograft tumor models, telomerase activity was abolished followed by growth arrest or apoptosis. Strikingly, the antiproliferative effect was delayed depending on the initial length of telomer et. Hence, it is not the direct telomerase inhibition which is relevant for cessation of proliferation, rather the loss of telomere function after significant telomere shortening. Recently, a novel structural class of non-peptidic, non-nucleosidic inhibitors of the catalytic component of telomerase was reported which demonstrates promising features for further preclinical evaluation [4]. A completely different approach is to exploit the preferential expression of telomerase for immunotherapies [5]. In fact, it has proved possible to induce a specific immune response against telomerase-positive cells by generating cytotoxic T lymphocytes directed at peptides derived from hTERT.

In summary, targeting telomerase appears to be very promising and widely applicable approach for tumor therapy in general, which impact, of course, can only be defined by following clinical studies.
2.3.6 Dendritic Cell (DC) Based Immunotherapy in Patients with Hormone Resistant Prostate Carcinoma in Combination with Interferon-Gamma

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Prostate carcinoma is the major cause of death in men between 50 and 60 years. No successful treatment options are available for patients with advanced stage of metastasized prostate cancer. Herein we report the design of a clinical trial addressing new options of immunotherapy for hormone refractory prostate cancer patients. Inclusion criteria are histological diagnosed prostate cancer in HLA-A2 positive patients with rising PSA after completion of hormone therapy displaying bone, lymph node or other metastases. For these patients dendritic cells are prepared according the regulations of good manufacturing practice after selection of CD14+ monocytes from autologous leukapheresis products. Monocytes are cultured under serum-free conditions with IL-4 and GM-CSF followed by IL-1, IL-6, TNF-alpha and PGE2 for a total of 7 and 3 days, respectively. Quality control is performed by two means: first, through FACS analysis of the immature and mature DC and second, on a functional bases employing a T2 cell based cytotoxicity assay. Mature DC are loaded with PSA derived peptides and three fractions of autologous DC are generated loaded with PSA1, PSA2 and PSA3 peptides, respectively. A total of 6 Mio peptide loaded mature DC are injected intracutaneously into the patient for a total of 4 immunizations in three weeks intervals. Patients are prepared for the immunization through the subcutaneous injection of 50 µg/m² Interferon-gamma two hours before application of the DC. Immune responses are monitored by three different assays: first, delayed type hypersensitivity is measured by a Merieux test in the skin of the patient before and after immunization; second, subpopulations of T-lymphocytes, NK-cells, B-lymphocytes and DC are quantified in the peripheral blood of the patient and third, the frequency of PSA peptide specific DC is determined through a Cytokine Secretion Assay based on antigen specific induction of Interferon-gamma production in peptide specific peripheral blood derived T-lymphocytes. Treatment effectiveness is measured through PSA level, size reduction of metastases and improvement of physical status. In summary, this clinical study is performed to determine the safety and efficacy of HLA-A2 positive autologous dendritic cells loaded with PSA derived peptides in combination with Interferon-gamma.

2.3.7 Idiotype Vaccination for the Treatment of Non-Hodgkin’s Lymphomas

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Normal and neoplastic B cells carry membrane-bound immunoglobulins as antigen receptors. The peptide sequences of these receptors are diversified by the rearrangement process of immunoglobulin gene segments and somatic hypermutation. As a result, unique sequences exist for each lymphoid clone, which are referred to as the ‘idiotype’ of each clone and represent clone-specific antigens. For over a decade, attempts have been made to generate specific immune responses against lymphoma-specific idiotypes.

In lymphomas with monoclonal gammopathies (multiple myeloma and lymphoplasmacytic immunocytoma), an idiotype vaccine can be produced simply by purification of the paraprotein from the sera of affected patients. In non-secreting lymphomas, soluble idiotype protein can be obtained by somatic cell hybridization of viable lymphoma cells with a permanent hybridoma cell line and purification of immunoglobulin from the cell culture supernatant. To generate a sufficiently immunogenic vaccine, the idiotype is commonly conjugated to the immunogenic carrier protein KLH and frequently injected with concomitant administration of GM-CSF. This type of idiotype vaccine induces protective, specific anti-lymphoma in a variety of animal models. In phase II clinical immunization trials conducted in patients with follicular lymphomas during clinical remission, induction of measurable anti-idiotype immune responses was associated with improved disease-free and overall survival. In addition, idiotype vaccination has been reported to result in the disappearance of minimal residual disease as assessed by sensitive PCR assays. Idiotype-presenting dendritic cells may represent an even more immunogenic anti-lymphoma vaccine. However, the superiority of this approach to first-generation idiotype vaccines has yet to be demonstrated.

Unfortunately, the considerable effort to manufacture individual idiotype antigen has hitherto prevented large-scale clinical testing. Therefore, our group has developed a rapid, PCR-based protocol for rapid expression cloning of lymphoma-derived immunoglobulin in E. coli.

A clinical Phase I immunization protocol with this recombinant idiotype vaccine is currently being conducted at our institution in patients with advanced B-cell lymphomas. In 11 patients vaccinated as of October 2002, the vaccine was well tolerated. Preliminary results seem to indicate the potential to induce idiotype-specific immune responses despite an overall immunosuppression due to previous antineoplastic therapies. While no clinical remissions could be documented, the majority of patient had stable disease during and after the scheduled vaccination course. Based on these phase I experiences, phase II trials for patients with low tumor burden and less suppressed immune status are being designed and may be initiated in the near future.

2.3.8 Immunotoxins in Cancer Therapy

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Recombinant immunotoxins consist of Fv regions of tumor-selective antibodies fused to toxins found in bacteria, plants or fungi. These toxins must be modified to remove normal-tissue binding sites, but to retain all other functions of cytotoxicity. The recombinant antibody fragments target the modified toxin to cancer cells which are killed,
either by direct inhibition of protein synthesis, or by concomitant induction of apoptosis. Cells that are not recognized by the antibody fragment, because they do not carry the tumor antigen, are spared. Many factors influence the in vivo anti-tumor activity of recombinant immunotoxins. Among them are considerations of which types of cancer may be the best targets for immunotoxin therapy as well as tumor specificity of the antigen that is targeted by the recombinant antibody. Other relevant issues are the affinity of immunotoxins and their ability to enter and penetrate into tissues and tumors, which in turn is dependent on the size of the protein. A great deal of protein-engineering is required to stabilize the recombinant antibody moiety of immunotoxins, since stability of the molecules is crucial for good clinical efficacy.

The task to deliver immunotoxins to solid tumors is much more difficult than for hematologic malignancies, since these tumor cells usually have tight junctions in-between, they show a heterogeneous blood supply and high interstitial pressure. Nevertheless some immunotoxins have recently shown efficacy in patients with solid tumors. LMB-1 (chemical conjugate of the monoclonal antibody B3 and a truncated version of the Pseudomonas exotoxin (PE38)) which targets the Lewisy antigen present on carcinomas of colorectal origin was tested in 38 patients in a phase I trial. Administered as a bolus infusion i.v. at 10–100 µg/kg one complete response and one partial response lasting 2 and 7 months respectively were achieved. The dose-limiting toxicity in this trial was the vascular leak syndrome (VLS). In order to achieve better penetration of the molecule and to achieve a shorter ‘connection’ time with the vascular wall the single chain (Fv) of this monoclonal antibody was fused to PE 38 (LMB-7). Due to common stability problems of single-chain molecules there were problems in reaching efficient concentrations of active immunotoxin in the tumor resulting in the lack of clinical responses. Therefore a disulfide stabilized version was constructed (LMB-9). Bolus as well as continuous infusion trials are still ongoing with LMB-9.

2.3.9 Suicide Gene Therapy for Cancer: What Have We Learned?


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The expression of genes in tumor cells encoding for foreign enzymes derived from viruses, bacteria or other mammalian species that are able to convert a prodrug with low systemic toxicity into a highly toxic metabolite is an experimental approach to treatment of malignant tumors. The aim of this strategy is to produce lethal concentrations of toxic metabolites in tumor cells expressing the therapeutic gene resulting in tumor cell death by apoptosis (cell-suicide). The destruction of non-transduced tumor cells surrounding a tumor cell expressing the suicide gene is called the “bystander effect” and is caused by the diffusion of toxic metabolites from the transduced tumor cell to adjacent cells. As compared to conventional chemotherapy systemic toxicity should be reduced due to low circulating levels of toxic metabolites. The therapeutic efficiency of various suicide genes has been demonstrated in vitro and in vivo in various animal tumor models, but expression of suicide genes in normal tissues may induce severe side effects. However, the first clinical trials of suicide gene therapy have shown the safety of this approach, but failed to demonstrate substantial therapeutic efficiency. Therefore further improvement of the efficiency of the suicide gene approach is mandatory. This includes improvement of gene transfer techniques to allow efficient expression of suicide genes in tumors. The commonly used replication deficient gene transfer vectors based on viruses such as adenoviruses, retroviruses or AAV are able to transduce a variety of tumor cells types in vitro, but the fail to allow efficient gene transfer into tumor tissue in vivo. This is mainly due to physical barriers such as the endothelial lining of the tumor vasculature and the enhanced tissue pressure in tumor nodules. Novel approaches aim at the development of vector systems, which can selectively replicate in tumor cells to allow spread of viral gene transfer vectors throughout the tumor tissue. To further improve the efficiency of suicide genes, the extent of the bystander effect needs to be enhanced. Current research is focused on the identification of new prodrug activating enzymes and alternative prodrugs to produce metabolites with enhanced toxicity and diffusion. In addition, mechanisms of tumor specific gene expression are under investigation to avoid expression of highly potent suicide genes in normal tissue. This may be achieved by the use of specific promoter sequences, which restrict gene expression to tumor cells. Finally, suicide genes may not only kill tumor cells by direct toxicity, but may also induce a potent antitumor immunity. The antitumor immunity induced by the suicide gene herpes simplex thymidine kinase (HSV-tk) is dependent on hsp70 upregulation during suicide gene induced cell death. Hsp70 may act therefore as an immunological danger signal resulting in the induction of a strong and specific cellular immunity against tumor associated antigens.

2.3.10 Macromolecular Prodrug Strategies: Exploiting Serum Albumin as a Drug Carrier for Cancer Chemotherapy

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Macromolecular prodrug strategies: Exploiting serum albumin as a drug carrier for cancer chemotherapy.

A new macromolecular prodrug strategy for improved cancer chemotherapy based on two features has been developed: (a) rapid and selective binding of thiol-reactive prodrugs to the cysteine-34 position of endogenous albumin after intravenous administration, and (b) release of the albumin-bound drug at the tumor site due to the incorporation of an acid-sensitive or enzymatically cleavable bond between the drug and the carrier. Development of a number of albumin-binding prodrugs demonstrates that the prodrugs are transported in their albumin-bound form and are distinctly superior to the parent compound in a number of animal tumor models. A hydrazone derivative of doxorubicin h(6-maleimidocaproyl) as been selected as a clinical candidate due to a favorable toxicity profile in mice, rats and dogs compared to doxorubicin (3- to 4-fold increase in MTD, lack of liver toxicity and immunotoxicity, transient effects on the lymphoreticular system).

2.4 Thoracic Malignancies

2.4.1 How Many Ribs Can Be Resected? Indication, Techniques and Results in Surgery for Chest Wall Tumors

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Introduction: Chest wall defects continue to present a complicated treatment scenario for thoracic and reconstructive surgeons. The purpose of this study is to report our 16-year experience with chest wall...
the controversial topic of ‘Lung cancer screening’ is present-the diagnostic work-up of a pulmonary nodule. Furthermore current diagnosis of the extent and localization of a potential malignant pulmonary nodule. Thin-section multislice spiral computed tomography which allows the solitary pulmonary nodule, with a particular focus on the role of contrast between aerated lung and pulmonary nodule. Precise diagnosis due to a decrease of partial-volume effect, thus improving for detection of pulmonary nodules increases with a reduction of slice particularly since the introduction of multislice spiral CT. Sensitivity be superior to chest radiography for detection of pulmonary nodules, CT is often necessary for detailed evaluation. CT has been shown to be superior to chest radiography for detection of pulmonary nodules, particularly since the introduction of multislice spiral CT. Sensitivity for detection of pulmonary nodules increases with a reduction of slice thickness due to a decrease of partial-volume effect, thus improving contrast between aerated lung and pulmonary nodule. Precise diagnosis of the extent and localization of a potential malignant pulmonary nodule is possible guiding the surgeon to lesions that are difficult to detect at surgery. The expanding availability and use of multislice spiral CT are although leading to increased numbers and decreased size of nodules detected. Diagnostic CT algorithms based on morphologic and density analysis are therefore warranted to guide the diagnostic work-up of a pulmonary nodule. Furthermore current data on the controversial topic of ‘Lung cancer screening’ is presented and discussed.

2.4.3
FDG-PET – a Cost-Saving Diagnostic Procedure in Oncological Thoracic Surgery?

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In the last decade positron emission tomography with 18F-Fluorodeoxyglucose (FDG-PET) has been introduced in the diagnostic of several malignancies with great success, among them lung cancer. Compared to other imaging methods the price of the examination is high. This depends most of all on the costs of the radiotracer that has to be produced on the very day of the examination due to the short half life time of the isotope. The production procedure requires a cyclotron and a radiochemical laboratory.

In times of very low budgets in public health care promising new diagnostic procedures have to prove that they are cost-effective and lead to improvement of medical standards. There are several publications showing that FDG-PET is more accurate than computed tomography (CT) for the staging of non-small cell lung cancer (NSCLC). A meta-analysis of more than 1000 Patients with NSCLC showed the accuracy of FDG-PET in the staging of patients [Hellwig, et al.: Pneumologie 2001]. Sensitivity and specificity reached 96% respectively 80% for the characterising of solitary pulmonary nodules, 88%/92% for lymph node staging and 94%/97% for the detection of distant metastases. In contrast to NSCLC FDG-PET data from patients with small cell lung cancer (SCLC) are rare. In a prospective study with more than 100 examinations we found PET results comparable to the staging of NSCLC. Summarized, the efficacy of FDG-PET for the evaluation of solitary pulmonary nodules and the staging of NSCLC and SCLC is well documented.

What about the cost-effectiveness? Considerable work evaluating the accuracy and cost-effectiveness of FDG-PET in characterising solitary pulmonary nodules has been performed in the US [Gambhir, et al.: Eur J Nucl Med 2000] and in Australia [Keith, et al.: Eur J Nucl Med 2002]. In agreement both publications show that FDG-PET is able to reduce costs and to extend life expectancy when it is carefully implemented in a baseline strategy. Due to the different costs structures of the health care in these countries the data are difficult to transfer to German conditions. However, for Germany it has also been demonstrated that the use of whole-body PET in the preoperative staging of patients with NSCLC and normal-size lymph nodes can save money [Dietlein, et al.: Eur J Nucl Med 2000]. The costs of the PET examinations were more than compensated by the more appropriate selection of patients for beneficial surgery. It has to be emphasized that although a PET strategy alone is a possible strategy to be considered, it is unlikely to gain clinical acceptance. It is more common that solitary pulmonary nodules are detected by CT or thoracic X-Ray first. In addition, most surgeons would prefer to have a CT scan prior to surgery for anatomical considerations. Furthermore, CT scans are helpful for biopsy when histological clarification is needed. Therefore, the considerable strategy of choice should be a combination of CT and PET. Where CT alone shows distant or lymph node metastases that excludes surgery PET scans are unnecessary. Otherwise, the advantages of FDG-PET increase the earlier the examination is used in the diagnostic process. For example, for patients undergoing FDG-PET to characterize a solitary pulmonary nodule additional information about the lymph node involvement and the metastatic spread in other organs is acquired at the same time and for the same price.

On the basis of the available studies countries like the US and Switzerland decided that several oncological indications for PET imaging have to be covered by public health care. In contrast, in Germany the public health provider refused reimbursement of PET examinations in general. The analysis of the cur-
current literature clearly shows that this German decision to reduce the medical standards is ethical doubtful and economical nonsense.

2.4.4
Who Wants to Perform a Pneumonectomy?
Parenchyma-Preserving Surgery
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Thoracic Surgery of bronchial carcinoma started by pneumonectomy in 1933. In the second quarter of the century, mortality for lobectomy and pneumonectomy was as high as 37 and 56%, respectively. In the time following, the proportion of pneumonectomy dropped down to 25%, whereas the mortality declined to about 10 percent [Wilkins 1978]. Nowadays, morbidity and 30-d mortality following surgery for lung cancer does not exceed 5%. Since the median age of the western populations raised continuously and the incidence of bronchial carcinoma multiplies with age (from 100 to 600/100.000 from 60y to 75y; Germany, 1995), the number of older patients, who need lung resection for bronchial carcinoma, is growing. Most of the patients with lung cancer are or have been smokers with impaired lung function. Since non operative treatment is low effective in lung cancer concerning long term survival, the thoracic surgeon has to develop methods of lung resection, which respects the comorbidity and the lung function of the patients.

Using bronchoplastic procedures, the surgeon cuts the main bronchus like in pneumonectomy but restore the function of distal lung. In our experience with 312 patients with bronchial carcinoma in stage I–IIIa we performed 194 pneumonectomies and 118 sleeve resections. The 30-d-mortality (4.6 vs. 5%) was not different. 5YSR in N0, N1 and N2 stage for pneumonectomy vs. sleeve resection were 42 vs. 50%, 33 vs. 39% and 11 vs. 21%. Whereas the prognosis of patients with N2-disease is determined by distant metastases, the radicalness of surgical resection is more important in N0-disease. The data support the use of bronchoplastic resections for lung cancer.

The use of segmental resections in lung cancer leads to a higher number of local recurrences (20 vs. 7%, LCSG 1995) and impairs long term survival. If for functional reason lobectomy is not feasible, the risk of the procedure and the oncological result has to be weight up. Since the rate of local recurrence rate rise to 50% after wedge resection of lung cancer, minimal invasive wedge resection is only advisable in patients with complicated emphysema.

2.4.5
Small Cell Lung Cancer: Is Resection Always Indicated?
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Normally, patients with SCLC are treated by chemotherapeutic and radiotherapy. In extensive disease the aim of therapy is palliation with a short time of survival (median 7–11 months). In limited disease the combined treatment with chemotherapy and radiotherapy of the thorax and the brain leads to 5-year-survival rates (5YSR) of about 5–10% and a median survival of 12–16 months. The role of surgery in patients with SCLC (limited disease) is denied, although there is some evidence of an advantageous effect on patients survival. Surgery alone does not influence the natural course of the disease. Retrospective studies of patients treated by surgery and adjuvant chemotherapy [Karrer 1989, Shepard 1991] reported 3YSR of 51% and 5YSR of 39%. This data are confirmed by our experience in 62 patients with SCLC between 1987 and 1997. 74% of the patients were operated first with adjuvant chemotherapy. Radical resection was possible in 88% by segmental resection (n = 5), lobectomy (n = 33), sleeve lobectomy (n = 9) and pneumonectomy (n = 14). 2 Patients died within 30 days postoperatively. Follow up was complete. 48% of the patients survived 5 years with a median survival of 33 months (c.i. 7–58 months). In a prospective study with preoperative radio-chemotherapy and following resection [Lad 1994] the authors found no difference between the two groups for the 5YSR. The number of studies in patients with SCLC is small. The resection of limited cancer and adjuvant chemotherapy seems reasonable with 5YSR comparable to the results in surgery for NSCLC. Since an important part of lung cancers consist of more than one histological type of cancer cells, secondary resection may be used in residual disease after chemotheraphy.

2.4.6
Small Cell Lung Cancer- Modern Chemo- and Radiation Therapy
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In the past small cell lung carcinoma was considered a curable illness due to the high remission rate after chemotheraphy. However, dependent on the stage of the disease, the length of time in remission is less than 1 year and more than 90% of patients relapse and die after a few months. The disease is already in a disseminated state by the time of first diagnosis, so that even at the start of treatment only systemic therapies can be considered. Etoposide, cisplatin, ifosfamide, cyclophosphamide, vincristin and doxorubicin are among the most commonly used conventional chemotherapeutic agents. The taxanes and topoisomerase I inhibitors are newer chemotherapeutic agents which are especially effective. A combination therapy induces a higher remission rate and leads to improved survival when compared to monotherapies. The combination of etoposide and cisplatin can be considered a gold standard for treatment, whereas in European countries combinations of cyclophosphamid, doxorubicin and vincristin (CAV) are preferred. Older protocols which involved the use of two or three conventional drugs could be seen as identically effective. In the limited disease stage (LD) it appears that the remission rate and median survival is improved by the addition of paclitaxel to cisplatin and etoposid, especially when radiation therapy is also performed. However, the importance of paclitaxel must be better defined through larger phase III studies. In contrast, the toxicity of the three drug regimens appears to outweigh any benefit in extensive stage disease. A combination of four conventional chemotherapeutical agents can slightly increase the remission rate but also lead to increasing toxicity, so that these protocols do not lend themselves to routine clinical use. Topoisomerase I inhibitors such as topotecan and irinotecan induce a high remission rate with tolerable hematologic toxicity. The combination of irinotecan and cisplatin at the advanced stage led to an improved remission rate and improved median survival. In small cell lung cancer with limited stage disease there should always be radiation of the primary tumor region, of the lymphnodes in the mediastinum and of the skull because of the high probability of a cerebral relapse. Early studies of simultaneous chemotherapeutic and radiation therapy show especially encouraging rates of remission and survival, so that in the future such a combination will be preferred for the group of patients with a good performance status. New principles of therapy such as tyrosine kinase inhibitors are currently being evaluated and open up new possibilities for therapy.
2.4.7

**Intensified Trimodal Treatment for Primary Inoperable Lung Cancer**

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Recurrent disease remains the major obstacle in the treatment of locally advanced lung cancer. Progress is expected when combining and intensifying different treatment modalities, though an increasing toxicity may result. It is the purpose of an ongoing phase-I trial of the Freiburg Center for Treatment of Thoracic Tumors to establish the basis for an aggressive trimodal treatment for patients with limited but advanced non small cell lung cancer (NSCLC).

Stage IIIA/B patients with histological proven NSCLC are eligible. They receive preoperative radiotherapy (RT, 63.4 Gy) along with i.v. cisplatinum (20 mg/m², days 1–3 and 28–30). Additional gemcitabine at escalating doses is administered every Friday during the RT course. Following reevaluation surgical resection will be performed.

So far 25 patients entered the protocol, 23 completed the preoperative therapy and 15 underwent surgery. At present 450 mg/m² gemcitabine is given weekly and dose-limiting toxicity has not been reached. However, one perioperative death occurred due to acute respiratory distress syndrome; this was not felt to be related to study procedures. Local recurrent disease did not occur so far. But eight patients suffered systemic relapse (8× brain, 4× liver, 3× bone, 1× adrenals, 1× nodes). Actuarial survival at one year is 63% + 10%.

It is concluded that aggressive local treatment eventually diminishes local recurrence of NSCLC and though the effect of intensification of gemcitabine on dissemination remains to be awaited for this trimodal therapy seems to be a promising approach for patients with locally advanced NSCLC.

2.4.8

**Chemosensitivity Assays and Microarrays towards Individualized Tumor Treatment**

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A long-term goal in oncology is the accurate prediction of treatment response to chemotherapeutic drugs. In general, the systemic treatment of tumors is based on clinical studies and relies on physicians’ empirical judgment. Although response rates of various anticancer drugs are well defined with respect to stage and histology of a given tumor, the effectiveness can vary significantly among individual patients. Methods to predict treatment response is particular of interest for tumors such as non-small lung cancer in which response rates for commonly used drugs are in the range of 20–30%.

For over 30 years, a variety of screening procedures have been established which are based on in vitro proliferation inhibition assays and on in vivo xenograft models. A systematic analysis of completed in vitro-in vivo correlative trials in 2,300 patients revealed percentages of 69% for true positives and 91% for true negatives from predictive assays [1]. Major disadvantages limiting the usefulness of these methods for clinical routine work are the slow turnaround and the limited growth potential of primary tumor cells in vitro. Recently, a novel chemosensitivity test, ChemoSelect® [2], has been described, which is a sensor-chip based diagnostic test and permits continuous real-time measurement of induced tumor cell cytotoxicity within 24 hours following the administration of chemotherapeutic drugs [2]. However, the efficacy of this methodology still needs to be evaluated in clinical trials.

A different way to predict chemosensitivity may rely on the emerging genomic and proteomic technologies, which allow to extract data of biomedical relevance for a wide range of applications. The microarray technology is a new and efficient approach that allows to analyze the expression of up to 20,000 genes in a tumor sample simultaneously. Using bioinformatic algorithms it has been demonstrated that a more accurate classification of tumors is possible which provides a complex molecular signature in addition to conventional histopathologic information [3]. Such molecular profiling might offer more accurate predictions towards prognosis [4] and molecular pharmacology [5]. Although progress in this field appears very promising, automated analysis procedures and prospective clinical trials are warranted to facilitate a genomic-wide approach to the way to individualization of patient treatment.


2.4.9

**Better – Faster – Further: Competence-Center for Chest Tumors**

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The institution of a Competence-Center for Chest Tumors is a logical approach aiming at accelerated diagnosis and treatment. It is also a natural result of traditionally very close interactions between the oncologic partners of a highly specialized clinical setting. Nearly two years ago it was possible to organize a joint outpatients’ venue with the participating four disciplines: the Departments of Medical Oncology, Pneumology, Radiology, and Thoracic Surgery in a single location. On referral every patient will be seen by one of the experts of the respective Departments. In most instances the pneumologist and/or the thoracic surgeon will be the ones who first get in contact with the patient in whom malignant disease is not yet proven, and in whom diagnostic identification is required. However, consultation with the partner disciplines from the beginning will provide the patient’s conviction that optimal care will be taken reflecting all available therapeutic instruments.

In particular, if patients from a geographically large area with long traveling distances have to be served the immediate multidisciplinary approach will save the patient a waste of time and inconvenience. The sequence of diagnostic procedures starting with bronchoscopy, sonography, thoracocentesis, etc. is put into an economical order avoiding delay and reducing costs. The interdisciplinary board allows for immediate second opinions and, automatically, challenges appropriate-ness of the individual proposals.

Once final decisions not only towards the diagnosis but, subsequently, towards the most effective treatment have been agreed upon the treatment is started either on an in- or an outpatients’ program. Co-operation between the involved experts must perpetuate once the primary treatment has been terminated. Aftercare as an instrument of patients’ welfare as well as quality control and source of scientific...
progress, again, is a joint venture providing important mutual information. Last but not least the maxime of the Competence Center must be to provide fruitful intercollegiate communication with the physicians outside at all times. Tight communication is contributing decisively to the quality of patient care and is an important factor helping to economize treatment of thoracic tumors. This is of utmost importance for maintenance of high standards despite increasingly limited resources. In a recent article Rintoul and Sethi [1] have used the phrase of ‘The Lung Cancer Paradox’ for the situation in Scotland. They deplore that in the U.K. the 5-year survival rate for patients with lung cancer is less than 5% compared to 14% in the U.S., the Netherlands, and the Scandinavian countries. Reason are low resection rates (10 vs. 25%) and lack of study programs. Devoted centers of competence for malignant tumors of the lung and the chest would be the desired answer in their opinion. This finds our entire agreement.


2.5 Stem Cell Transplantation

2.5.1 Hematopoiesis and Different Stem Cell Sources

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All blood cells originate in a small number of undifferentiated stem cells (HSC) that normally reside in the bone marrow but can be mobilized into the peripheral blood by administration of cytotoxic drugs as well as hematopoietic growth factors or cytokines. Until now a specific phenotype of human HSC could not be defined. Detection and quantification of HSC has therefore to rely on retrospective assays testing functional properties assigned to them: a high proliferative potential, multi-lineage differentiation and longevity. Different in vitro assays were designed to enumerate stem cells in transplants including direct colony formation after growth factor stimulation in semi-solid medium (colony forming cells, CFC) or after extended co-cultures with bone marrow stroma cells (long-term culture initiating cells, LTC-IC). More recently, the observation that severely immunodeficient mice and pre-immune fetal sheep support the homing and differentiation of human hematopoiesis allowed to establish different xenotransplantation models for human transplantable cells. Using NOD/SCID-b2m-deficient mouse hosts heterogeneity in the human transplantable stem cell compartment was revealed. Kinetic as well as cell purification studies suggest that hematopoietic reconstitution in humans is dominated by different types of short-term repopulating cells during the first months after transplantation. Myeloid-restricted short-term repopulating cells play a major role during the first month after transplantation and are followed by a second type of short-term repopulating cell able to regenerate myeloid as well as lymphoid lineages for a still undefined period of time. Comparative analysis demonstrated that mobilized peripheral blood transplants are largely enriched in both types of human STRC as compared to bone marrow and even more strikingly to cord blood transplants suggesting that the faster hematopoietic reconstitution after transplantation of mobilized peripheral blood as compared to bone marrow can be assigned to a higher amount of STRC. Gene marking studies underlined the importance of STRC for the early hematologic recovery in patients. A specific use of well-defined purified or ex vivo differentiated STRC would allow to reduce post-transplant toxicity.

2.5.2 Allogeneic Hematopoietic Cell Transplantation: How Much Conditioning and How Much Graft versus Tumor Effect?

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The initial underlying therapeutic principle of allogeneic bone marrow transplantation was to treat patients that had hematologic malignancies with intensive chemoradiotherapy intended to completely eradicate neoplastic cells, and then to rescue the patients from the regimen-induced bone marrow aplasia with infusion of hematopoietic stem cells from healthy donors. Analyses of preclinical and clinical data, however, revealed a second powerful therapeutic effect of this approach – the graft versus tumor effect – in which lymphocytes contained in the donor graft recognize the leukemia cells as foreign and kill them. There is now evidence that the graft versus tumor effect is explored not only against leukemia cells but also against non-hematopoietic cancers such as renal cell, breast, ovary or colon cancer. Graft versus tumor effects form the therapeutic basis of recently developed less intensive conditioning protocols known as non-myeloablative, ‘mini’-transplants. These rely less (or not at all) on chemoradiation tumor eradication and shift the burden of tumor cell killing towards graft versus tumor effects. The first developed ‘mini-transplant’ regimens were based on reduced intensity versions of conventional regimens. The new ‘mini’-transplant approaches use immunosuppressive drugs (or low dose irradiation) intended to prevent rejection of the transplanted hematopoietic stem cells. The lack of regimen-related toxicity associated with this approach has permitted the extension of allogeneic hematopoietic cell transplantation (HCT) to include both elderly and medical infirm patients who were not eligible for conventional transplants. Thus, efforts in understanding the power of the graft versus tumor effect and efforts in establishing new low intensity conditioning regimes have changed the role of allogeneic HCT from a desperate therapeutic maneuver, performed only in young patients with leukemia, to a standard curative treatment for various hematologic malignancies, eligible in all patients with no age restriction, as well as a promising curative approach for metastatic cancer.

2.5.3 Graft-versus-Host Disease (GvHD): Clinic, Prophylaxis and Therapy

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Graft-versus-host disease, the reaction of the donor immunosystem in allogeneic transplantation against the tissue of the recipient, is a T-cell reaction and welcome in a limited measure. Because often the graft-versus-Leukaemia/Lymphoma [GvL] effect occurs besides GvHD, necessary for the immunologic eradication of the malignant clone. GvHD occurs at 3 different time points after transplantation, involving different organs and with different clinical and histopathologic pictures. Hyper-acute and acute GvHD develop during and after engraftment till day + 100; an acute inflammation of the recipients tissue especially involving skin, soft tissue of the whole gastro-intestinal tract, liver and biliary tract system. In accordance with the degree of skin involvement, amount of diarrhea and the value of ALT/AST and bilirubin four different grades are defined as ‘I–IV’. Acute GvHD >‘II needs an intensification of the immunosuppressive therapy and grade III/IV are often refractory to high dose immunosuppression.
2.5.4 Infections and Immune Reconstitution – How Important are T-Cells?

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Infections are a major cause of mortality after stem cell transplantation. The increased susceptibility for infections is based on complex alterations in the host defense. The extent and degree of such alterations depend on the type of transplantation performed and the degree of the immune reconstitution. Therefore, the susceptibility for certain infectious agents varies with the type of transplantation and the time passed after transplantation. The early phase after transplantation with a myeloablative conditioning regimen is characterized by neutropenia, which favors bacterial and fungal infections. Also, the susceptibility for infections with the herpes-simplex-virus and respiratory viruses is increased. After engraftment, viral infections, especially by cytomegalovirus (CMV) and adenovirus predominate, because of the still insufficient reconstitution of the T-cell system. The extent of T-lymphocyte dysfunction and therefore the extent of the susceptibility against viruses is increased by graft-versus-host disease and the immunosuppressive therapy needed. Also, patients with less intensive conditioning regimens are susceptible to viral infections because of the increased immunosuppression applied in order to sustain engraftment. CMV disease is associated with a high mortality. However, the introduction of prophylaxis or preemptive polymerase chain reaction (PCR) and antigens guided therapy with ganciclovir has decreased the incidence of CMV-disease. The transfer of ex vivo generated virus-specific donor T-cells offers a new promising approach which has already shown to be successful in the prevention and treatment of infections with CMV, Epstein-Barr-virus (EBV) and adenovirus.

2.5.5 Extracorporeal Photopheresis (ECP) in Cutaneous Graft versus Host Disease (GvHD)

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Acute and chronic cutaneous Graft versus Host Disease (GvHD) is the most frequent complication of bone marrow transplantation occurring in the skin. Recently, the excellent therapeutic efficacy of Extracorporeal Photopheresis (ECP) in patients with acute or chronic GvHD has been demonstrated. This novel therapeutic modality will be explained in detail and results of children and adults with acute or chronic GvHD treated successfully by Extracorporeal Photopheresis will be presented and discussed.

2.5.6 Graft versus Host Disease – Treatment Strategies in Severe Dry Eye Syndrome after Hematopoietic Stem Cell Transplantation

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Recent advances of stem cell research have decisively influenced the treatment of malignant hematopoietic diseases. Side effects of treatment and graft versus host reaction lead to new eye diseases, which might have considerable influence on the quality of life of the affected patients. Graft versus host disease may cause severe dry eye syndrome. However, new treatment strategies are successful and may even help in the treatment of other more frequently seen autoimmune diseases. The clinical diagnosis of graft versus host reaction against the eye is based on the characteristic and frequent blinking, on the chemosis and the typical subtarsal conjunctival scars. Furthermore, break up time, fluorescein-, bengalrosa and Schirmer tests are important as well as the histological examination of biopsy specimens. In order to improve the treatment a mucus deficiency syndrome induced by the graft versus host reaction should be differentiated from Sjögren-like dry eye syndrome. Treatment should be modified depending on the severity and staging of the disease by (I) intensifying tear supplementation, punctum occlusion and use of high polymeric hyaluronic acid eye drops, (II) in case of histological proven graft versus host reaction by stepwise local immunomodulation with steroids and/or cyclosporin and (III) in case of signs of aggressive general extension of the graft-versus-host reaction by intensifying the systemic immunosuppressive therapy e.g. by extending the treatment, increasing the dose or adding further immunosuppressive drugs. Adequate treatment can minimize the side effects of the systemic therapy, can prevent severe corneal complications and can improve quality of life and professional reintegration of the patients.

2.5.7 Indications for High-Dose Chemotherapy (HDCT) and Autologous Hematopoietic Stem Cell Transplantation (ASCT)

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HDCT and ASCT have increased during the last decade and have become an accepted therapy option for many diseases, including lymphoid, selected hematological and solid tumor malignancies. Stem cell
source and indications have changed. Information on these changes is essential for interpretation of current data, patient counseling and health care planning. Especially intermediate- or high-risk as well as relapsed lymphoma (L) have shown impressive response rates, therefore, ASCT is increasingly used in chemosensitive or refractory non-Hodgkin’s (NHL), Hodgkin’s lymphoma (HD) and multiple myeloma (MM) patients (pts) [1–3]. Other indications are high-risk germ cell tumors (GCT) [4], chemo-responsive sarcoma (S) [5], certain indications in acute myeloid leukemia and severe autoimmune disease [6]. Over the last years the frequency of L pts (including those with systemic AL amyloidosis) has increased, but has declined in breast, lung and ovarian cancer [7]. The preferred stem cell source nowadays is peripheral blood over bone marrow in > 99% of pts [1]. Options to stratify pts most likely to benefit from ASCT are according to the international prognostic index (IPI) risk factors in NHL (which include stage III/IV disease, age > 60 years, elevated LDH, decreased performance status and extranodal disease). HDCT and ASCT are especially beneficial for pts with an IPI-status > 2 [8]. Results in relapsed HD have demonstrated that durable remissions are obtained after ASCT, even in multiple relapsed HD. In MM, single ASCT have led to improved remission rates and prolonged survival, although pts may eventually relapse. Therefore, tandem ASCT are performed in standard-risk pts (as defined by normal cytogenetics), and single ASCT followed by allogeneic transplants in those with 13q deletion. The tandem autologous and the autologous-allogeneic-transplant protocols are effective and provide rapid engraftment with tolerable toxicity. In pts with systemic amyloidosis, ASCT can be an effective and safe treatment option if performed before the manifestation of irreversible and treatment-limiting organ damage. In S pts, especially those with multifocal primary, relapsed or metastatic disease, ASCT can result in impressive remission rates. According to our own data, long-term survival appears favorable for, or even restricted to, those S pts showing a PR or CR following induction and high-dose treatment. ASCT in S responders may be a possible substitute for radical operations, but needs to be further assessed in prospective clinical trials. As in advanced or relapsed GCT, ASCT is also effective, and single as well as tandem transplant options are being studied. The transplant-related mortality with HDCT and ASCT remains low and is continuously decreasing [1]. According to our and world-wide results, ASCT is curative for 20–80% of pts, especially in primary high-risk and relapsed aggressive L, also largely depending on the status of disease prior to transplantation. After CD34+ selected ASCT, higher age (> 50y), decreased CD34+ numbers (< 4¥10e6/kg) and high-risk L pts are risk factors for infectious complications, so that the effective removal of mature T- and B-lymphocytes bears a risk for delayed immune reconstitution. Here, prolonged antiboiphil prophylaxis, close lymphocyte monitoring and specific approaches to enhance immune reconstitution should be useful in reducing the danger of opportunistic infections. These result suggest that ASCT is beneficial in the disease entities mentioned above. Pts well responding before (and after) ASCT are curable. Those with no response before ASCT have reduced survival rates and may benefit from novel strategies, including use of innovative chemotheraphy agents, antibody-based therapies, in vivo purging, treatment of minimal residual disease post ASCT and/or use of allogeneic transplantation.

2.5.8 Stem Cell Transplantation for Congenital Disorders – When to Transplant Which Patient?

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Besides hematological malignancies congenital disorders are an important indication for allogeneic stem cell transplantation (SCT) in children. Congenital disorders include inborn metabolic errors, immunodeficiency syndromes and congenital bone marrow failures. For some of these diseases like severe immunodeficiency syndromes SCT is the only effective treatment. The lack of alternative treatment modalities and the limited prognosis without SCT justifies the risk of SCT from any donor available. To avoid infectious complications SCT should be performed as soon as possible. In contrast, patients with thalassemia can be treated with regular transfusions combined with chelation therapy. This treatment, although not curative, avoids the consequences of ineffective hematopoieses and iron overload due to transfusion. However, only SCT is curative, but bears the risk of transplant related mortality and rejection. The risk of SCT depends on the type of donor and previous treatment. Transfusion therapy and related iron overload increases the risk of SCT. In conclusion, patients with a matched sibling donor should be transplanted early, whereas the high risk of SCT with an unrelated donor is generally not justified for patients with thalassemia.

For congenital neutropenia SCT is the only curative treatment, too. But more than 90% of these patients can successfully be treated with G-CSF. With this treatment the patients are free of infections, but still have the well known risk to develop myelodysplastic syndrome or acute myelocytic leukemia. About 10% of the patients develop this complication. In this stage of the disease SCT is the only effective treatment, but the survival rate is low. If SCT is performed earlier in the course of the disease the probability of survival is higher. To identify patients at risk to develop MDS/AML bone marrow aspirations including cytogenetics and the analyses of G-CSF receptor mutations should be performed annually. Because the G-CSF receptor mutation is one step towards the development of malignancies, the risk of SCT may be justified as soon as they appear.

In summary, therapeutic decisions for patients with congenital disorders must be carefully taken. The risk of SCT depends on the type of donor, the previous treatment and the stage of the disease. It has to be compared with the possibilities of alternative treatment modalities.

2.5.9 Acute Lymphoblastic Leukemia (ALL) in Children and Adults – for which Subgroups Can Allogeneic Stem Cell Transplantation (SCT) Be Recommended?

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Treatment of ALL has improved considerably during the last 25 years. Currently, about 70% of children and 40% of adults can be cured from their disease with conventional chemotherapy only. Considering these cure rates, it is obvious that SCT can only be considered for subgroups of patients with high-risk disease. The risk of treatment failure with chemotherapy alone has to be weighed against transplant-related mortality and morbidity. The latter strongly depend on the kind of donor available. The degree of HLA-matching of the donor influences the toxicity of preparative regimens and the risk
of severe graft versus host disease (GvHD). Therefore, recommendations for SCT in ALL have to consider the risk of relapse and the kind of donor available.

One of the most important risk factors for treatment failure is response to chemotherapy in vivo. This can be measured by response to individual drugs like steroids, the time to achieve morphological remission and the kinetics of minimal residual disease (MRD), e.g. quantitated by PCR of clone-specific T-cell receptor or immunoglobulin gene rearrangement. In the German pediatric studies BFM-ALL, high risk features are defined as poor response to a 8 day steroid pre-phase (prednisone poor response), absence of morphological remission on day 33 of induction therapy and/or MRD on days 33 and 52 of therapy. In addition to response to therapy in vivo, the presence of certain molecular aberrations in leukemic clones influences therapy. The translocation t(4;11) and t(9;22) are associated with poor outcome with chemotherapy only. While immunological subgroups like T- or pro-B cell phenotype by themselves are of minor prognostic importance in the pediatric studies, they can heavily influence prognosis if considered in the context of response to therapy or molecular aberrations. In the pediatric BFM-ALL studies, absence of morphological remission on day 33 justifies matched or mismatched related or unrelated SCT. The same is true for MRD on day 52 of $>10^{-3}$. In case of MRD on day 52 at a level of $10^{-3}$ only completamente matched related or unrelated SCT is recommended. For patients with translocation t(4;11) and prednisone good response, results of chemotherapy alone are superior to those of SCT. If there is poor response to steroids and t(4;11), dismal outcome is currently not improved by SCT. In contrast, SCT significantly improves outcome for patients with translocation t(9;22). Recommendations for ALL with t(9;22) include unrelated matched donor SCT even in the presence of prednisone good response. For prednisone poor response and t(9;22) mismatched donor SCT is appropriate. In conjunction with prednisone poor response immunological T-cell phenotype or pro-B phenotype or M3 morphology (> 25% blasts) of bone marrow on day 15 or an initial white blood cell count of 100 000/µl or more are further risk factors that justifi SCT with an HLA-identical related or unrelated donor.

In adults, SCT is given a high priority. Study GMALL 06/99 currently recommends SCT for all patients with high risk ALL. These are B precursor ALL with complete remission after day 24 of therapy or initial white blood cell count of $>30 000/µl$ or pro-B ALL or t(4;11) positive ALL or early or mature T-ALL. Patients with t(9;22) have been assigned to a very high risk group and should also be treated with SCT. In the absence of an allogeneic donor autologous SCT is to be performed. Standard risk patients receiving chemotherapy for one year can qualify for SCT depending on results of MRD. Recommendations for SCT will have to be re-evaluated on a regular basis because they have to account for both, improvements achieved with chemotherapy and with SCT.

2.5.11 Outpatient Care after Allogeneic Transplantation

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After engraftment or after discharge from the transplantation unit patients care is not finished. He may afterwards experience a lot of complications. These should be recognized early and avoided by preemptive diagnostic and early therapy. Most important is the cooperation between transplant center, transferring clinic and family doctor. Before discharge the patient receives an intensive training to inform the transplant-center in case of: fever, skin changes or diarrhea. In the first 3 months close visits of the patient in the outpatient department of the transplant center is recommended, later the time intervals depend on the clinical situation. The primary goal is the continual reduction of the immunosuppression to give the donor immune-system the opportunity for an intensive Graft-versus-Leukemia/Lymphoma [GvL] effect. Parallel to the reduction of the drugs there is a risk to develop Graft-versus-Host Disease (GvHD), the reaction against the tissue of the recipient. A mild GvHD-reaction is desirable, because the GvL effect correlates with the GvHD reaction. GvHD may become a dangerous, chronic disease with isolated organ toxicity (e.g. eye, lung, liver, skin). Therefore in the first months the immunosuppressive medication will be periodically tapered. GvHD prophylaxis depends further on the pre-transplant remission and the donor/recipient chimerism after transplantation. In case of mixed chimerism, the immunosuppression will be reduced faster to achieve a complete chimerism. Regular disease specific diagnostic procedures (bone marrow, FISH examination, molecular diagnostic, MRD, PET, CT-scan) will be performed to control remission. Depending on conditioning regimen, kind of graft (T cell depleted or not) and immunosuppression the patients are at risk for live threatening infections. These are especially herpes virus reactivation (CMV or VZV) or opportunistic infections like pneumocystis carinii or toxoplasmiasis. Screening diagnostic on regularly basis and preemptive therapy should avoid severe infections. 6 to 12 months after transplantation the patient will receive multiple vaccinations, especially against pneumococcus spp. and haemophilus influenza. The goal of the transplantation, cure of the patient with an high level of quality of life, can only be achieved by close care and intensive cooperation between patient and his caretakers.
2.6 Skull-Base Surgery

2.6.1 Introducing Freiburg’s Center for Skull Base and Craniofacial Surgery

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For the successful treatment of complex pathological conditions of the skull base – mostly tumors, traumatic lesions and congenital or vascular malformations – an integrated approach of different disciplines is necessary. Therefore, the Departments of Neurosurgery, Otolaryngology, Oral & Maxillofacial Surgery, Radiation Therapy, Neuroradiology and Ophthalmology have joined to found the Center for Skull Base and Craniofacial Surgery. The center’s main objectives are the establishment of an optimized organizational schedule for treatment planning as well as the development of sophisticated surgical approaches and employment of newly developed technical devices, such as computer-assisted surgery or robotics. Important columns for the success are the organization and realization of scientific projects, the training of young colleagues, continuing education and the cooperation with partners in academics and industry. Altogether this should provide the best conditions to turn new concepts into practice. Three important elements form the nucleus of the Center for Skull Base and Craniofacial Surgery: Through the special Skull Base Referral and Appointment Service, new patients are selected and the necessary diagnostic tests arranged for presentation at the Skull Base Conference. It also organizes eventual postoperative treatment modalities, ambulatory follow-up appointments and evaluation of the results. At the Skull Base Conference, representatives of the various disciplines come together to discuss the patient’s case, further diagnostic options and develop the treatment plan. For interdisciplinary surgical interventions, a specially designed Operating Room is available, equipped with an array of different systems for computer-assisted surgery as well as all the necessary instruments for the various surgical disciplines. Based on the experience so far, the concept of an institution, where all the different disciplines working in the field of skull base and craniofacial surgery concentrate their expertise, has been a success. The center provides the framework for an adequate patient care. Main focus for the future will be to extend the range of computer-assisted surgical techniques. In cooperation with industrial partners, the suitability of robotics for employment in the area of the skull base should be evaluated.

2.6.2 Diagnostic and Interventional Neuroradiology in Lesions of the Skull Base

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The anatomy of the skull base is complex. The skull base is composed of the ethmoid, sphenoid, and occipital bones and the paired frontal and temporal bones. It can be divided into the anterior, the middle, and the posterior cranial fossa. Besides the bony structures with a lot of normal variants the complexity of this region increases with the surrounding structures of the dura and the brain, cavernous sinus, the orbit, the paranasal sinuses, and the soft tissue below the skull base. Lesions of the skull base include a broad variety of etiologies (e.g. benign or malignant tumors, metastases, inflammations, aneurysms, dysplasias). Some tumors have a strong tendency to arise at a particular location and almost never occur in other regions (e.g. chordoma, chondrosarcoma, esthesioneuroblastoma). Other tumors, such as meningiomas or metastases, can occur almost anywhere at the skull base. CT is the imaging modality of choice to depict bony destructions and pathological calcifications. Soft tissue changes are best imagined by MRI. Advanced MR techniques as fat suppression or MR-angiography may give further information on lesion extent and characteristics. Preoperatively a diagnosis often may be suggested by combining clinical data, anatomical location, and imaging characteristics. With the advent of new surgical and focused radio-surgical treatments, the precise definition of the extent of a lesion is of clinical importance. For this purpose, in addition to routine MR- and CT-scans, 3D data sets may be acquired for navigated surgery. 3D data sets of CT and MR examinations can be fused for exact preoperative planning and for the intraoperative use.

Due to the advances in CT and MR technology, infra-arterial angiograms for diagnostic purposes of tumors are only seldom necessary. However, in highly vascularized lesions (e.g. meningiomas or glomus tumors) preoperative endovascular embolization may reduce blood loss during the following surgery. In patients with tumor in close contact to the internal carotid artery (ICA), preoperative temporary balloon occlusion is used to test whether a permanent occlusion of the vessel will be tolerated. Thus, in selected patients interventional neuro-radiological procedures will be part of a interdisciplinary therapeutic approach.

2.6.3 Computer Aided Skull Base Surgery: Future Aspects

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Computer aided skull base surgery today consists of the use of computer based preoperative imaging methods (e.g. Computed Tomography (CT), Magnetic Resonance Imaging (MRI)), the preoperative use of 3-D planning systems and the intraoperative use of surgical navigation systems. According to the exploding capabilities of computer systems, the capabilities of planning- and navigation devices have constantly improved. Especially in skull base surgery, with the direct and narrow neighborhood of bony structures, vessels, nerves and the brain, preoperative planning systems using high resolution 3-D datasets allow simulation of various surgical approaches. As a result the surgeon can develop the optimal concept for the pathomorphologic conditions of the particular patient. Surgical navigation can provide this preoperative plan and additional information for intraoperative orientation. Nowadays these techniques are routinely used. Robotic systems have shown their accuracy in the industry. The combination of exact preoperative planning with the accuracy of a robotic system should result in further improvement of the surgical therapy of skull base tumors. In our center we evaluate the possibilities of navigated robotic systems for surgical procedures on bony structures of the skull base.
2.6.4

**Computer-Assisted Surgery in Management of Lateral Skull Base Tumors**

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The lateral skull base is of vital importance in static and functional respects. Therefore, resections should always be performed considering anatomic and functional results. Cosmetic aspects are highly important for the quality of life for most patients, as well, and have to be considered, too.

In our Skull Base Center, computer-assisted surgery has been well established in regard to resection and reconstruction. Before the onset of surgery, planning can be performed on a computer, and potential interdisciplinary actions are coordinated. Trepanation points and surgical corridors are discussed on the computer screen and may be objectively realized in the operation theater. Intraoperatively, tumor formations can be visualized and controlled objectively. Crucial organs (e.g., the internal carotid artery) can be safely localized and saved anatomically and functionally.

In the reconstructive phase of surgery, an objective visualization of the original anatomic contours is possible, thus improving optimal static, functional, and cosmetic results.

2.6.5

**Surgical Rehabilitation Following Facial Palsy**

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Surgical procedures at the lateral skull base may generate temporary or permanent dysfunctions of the facial nerve. In contrast to other cranial nerves, dysfunctions of the facial nerve are immediately visible to everybody. This is one distinct reason for surgical rehabilitation because patients with postsurgical, idiopathic or traumatic dysfunction of the facial nerve are highly interested in procedures rehabilitating the facial nerve function. Basically we distinguish dynamic from static facial nerve plastics. There is a pool of surgical procedures of dynamic and static facial nerve plastics. In general, surgical dynamic facial nerve plastics are characterized by a reanastomosis of the injured facial nerve to another intact cranial nerve. This may be the lower radix of the hypoglossus nerve, a crossover anastomosis to the contralateral intact facial nerve, or a local or free transposition and fixation of an innervated muscle like maseter, temporalis or suralis muscle to the paralyzed mimic muscle system. Static facial surgical plastics procedures are the upper lid implants made of gold or platin, fascia lata grafts to correct the mouth angle or facial skin retraction in the nasolabial angle. Impact, indications, surgical procedures and complications will be demonstrated by means of selected surgical cases.

2.6.6

**Outpatient Clinic for Skull Base Surgery: Keeping in Contact with the Patient**

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The purpose to provide a special outpatient clinic for patients with lesions of the skull base is to offer the patients a center of competence for the treatment of these complex diseases.

The first preoperative contact is usually shortly after the diagnosis of a skull base tumor. During this first visit we check, whether this particular patient is really going for skull base surgery and gather all the information we need to decide whether there may be alternative strategies for the treatment of the tumor. With this information the patient is presented to the weekly conference of the center for skull base surgery. This interdisciplinary conference decides about the treatment options, which are proposed to the patient. With the next contact the patient is advised according to the conference’s decision and scheduled for the particular department.

The first postoperative visit is usually scheduled 3 months after the operation. The patient presents pre- and postoperative scans. The wound is inspected and the patient is checked for persisting postoperative sequels. If necessary, the patient is presented to the interdisciplinary conference of the center for skull base surgery again, to discuss and schedule adjuvant therapy.

The patients keep in contact with the clinic through yearly visits with current MR scans. Through this ongoing contact with the patients, recurrent tumors or progression of remaining tumors can be detected early, so that additional therapy can be planned in time.

This interdisciplinary concept provides the patients with all the treatment options available for their particular tumor and thus gains the patients' confidence.

2.7 Rehabilitative Onkology

2.7.1

**Therapeutic Goals in Breast Cancer Rehabilitation: Preferences, Patterns and Predictors for Outcome Measures**

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Therapeutic goals in oncological rehabilitation programs are very heterogeneous. Interdisciplinary rehabilitation programs take into account all medical, physiotherapeutic and psycho-social aspects of oncological aftercare. Quality of Life (QoL) assessment is today’s best method to evaluate these programs, because QoL instruments cover a broad range of outcome domains. Depending which therapeutic goals are indicated, the concordance of individual goals and outcome domains could vary and treatment effects could be underestimated in studies with multiple QoL endpoints. The purpose of the ZESOR study was to evaluate the effectiveness of oncological rehabilitation programs under controlled conditions and to explore the association between goal setting, goal attainment and treatment outcomes. A new instrument for assessment of rehabilitation goals in patients with curative breast cancer was developed. Ten domains of breast cancer-specific goals were identified. In a sample of 361 women, individual therapeutic goals were interactively assessed before rehabilitation and evaluated after treatment. EORTC QLQ-C30 and breast module were used for QoL assessment and HADS to assess emotional state before and after treatment. Multivariate analyses showed statistical and clinical significant improvements over time. Comparative analyses between women participating in rehabilitation programs and women who do not, showed advantageous effects in the domains emotional functioning, anxiety and fatigue. Analyses of therapeutic goals demonstrate the key aspects of treatment goals and expectations for women participating in rehabilitation programs. Distinct patient subgroups with specific treatment needs could be identified.
Goal attainment analyses revealed patient subgroups with high and low rehabilitation benefit. High goal attainment scores in the domains information, symptom control, psychological issues and physical functioning/exercise were found as good predictors for beneficial rehabilitation outcomes. Our findings demonstrate, that the systematic assessment of rehabilitation goals is an important method to identify individual target domains and to prioritize treatment goals in oncological inpatient rehabilitation.

2.7.2 Rehabilitation After Hematopoietic Stem Cell Transplantation

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Since 1993 we established at the Tumor Biology Center in Freiburg a rehabilitation program for patients after allogeneic or autologous stem cell transplantation (HSCT) in close cooperation with the transplant center of the I. Medical Clinic of the University of Freiburg. Since 1993 more than 1300 patients participated at this program. About 60% of the patients had an allogeneic transplantation. Most of them had been transplanted in transplant centers of southern Germany. The presentation will focus on the 9-year experience with this specific rehabilitation program. As an initiative of our group a nationwide panel of experts in transplantation and rehabilitative medicine has been established in 2001 to formulate recommendations and guidelines for this area. Further, the results from an outcome study on the socioeconomic status of 419 patients, treated since 1996 will be presented.

2.7.3 Neuropsychological Training Programs in Oncological Rehabilitation: Possibilities and Limits of Cognitive Treatment

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The issue of cognitive impairment as a possible side effect of oncological treatment strategies has been neglected in psychooncology for a long time. Along with improved curative effects and longer survival times, interest has grown regarding aspects of patients’ quality of life and the need for goal-oriented oncological rehabilitation. In this context the issue of cognitive deficits and their remediation in tumor patients will be discussed.

There is growing evidence for the possibility of cognitive impairment as a short and probably long term therapy side effect in cancer patients with tumor diseases and treatment strategies not primarily affecting the central nervous system (CNS). An overview on the empirical literature will be given in our presentation in the symposium on psychooncology. Although the empirical data base is still poor and many theoretical aspects are still unclear, professionals in oncological rehabilitation express their growing awareness of the problem and the need for empirically evaluated treatment strategies. Up to date, there have been no such attempts relating to adult cancer patients, and the few publications in the area of pediatric oncology cannot be simply applied to this group.

Currently, we are conducting a study granted by the “Bundesministerium für Bildung und Forschung” (Federal Ministry of Education and Research) and the “Verband Deutscher Rentenversicherer” (Association of the German Pension Insurance Companies) in the Tumor Biology Center, Freiburg, in order to examine the effects of intensive cognitive training in an inpatient rehabilitation unit.

Patients after allogeneic hematopoetic stem cell therapy (HSCT) and breast cancer patients after adjuvant chemotherapy for whom cognitive deficits after treatment are described in the literature are covered by our study program. According to the current state of knowledge, our diagnostic and therapeutic strategies are primarily directed at attentional processes and certain aspects of amnestic functioning, especially short-term and working memory. The criterion for cognitive deficit is defined on the results of three computer-based tests of attentional processes. Patients meeting our criterion are randomly assigned to a PC-aided training program or a group conducted by a specially trained occupational therapist. Patients take part in four 60-minute training sessions per week under both conditions.

It is planned to include 70 patients in each training group, with the same number of patients from the two diagnostic groups. Patients who meet our criterion but refuse to participate in the training program serve as a control group if they agree to take part in the three test evaluations. In addition, the treatment groups will be stopped for certain time intervals in order to create a control group of the same size.

Neuropsychological examination is supported by the assessment of patients’ self perception of cognitive problems in daily life, quality of life, cancer-related fatigue and current affective status. A second examination, using the same test battery, is carried out at the end of the rehabilitation stay to assess short time effects of the training program. As a further step we are planning for catamnestic evaluations to be carried out six months later.

The presentation will focus on the diagnostic and therapeutic strategies applied in our study as a starting point for the discussion of methodological issues in the planning of cognitive rehabilitation programs for tumor patients; furthermore we will present preliminary data from a pre-study on the short-term effects of our training program.

2.7.4 Prospective Randomized Placebo Controlled Trial for the Treatment of Polyneuropathy Induced by Chemotherapy

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Neurotoxic side effects, especially the peripheral polyneuropathy (PNP), is a frequent problem following certain cytostatic therapies. Quite frequently the related – sometimes significant – constrictions determine after a completed therapy the quality of life of the patients. Effective prophylactic measures reducing neurotoxic effects do not exist yet. Up to now there are no established standards for the treatment of a cytostatic induced PNP although this undesirable effect frequently shows up for certain classes of substances and partly limits the applicable dose. The effectiveness of different empirical methods of treatment has not yet been evaluated. Therefore in a prospective randomized placebo controlled pilot study with 60 patients the effectiveness of different treatments for peripheral polyneuropathia after a completed chemotherapy with Vinca alkaloids, taxans and/or derivates of platinum has been investigated. The patients were divided among four groups of 15 patients each: treatments with electrostimulation-acupuncture, hydroelectric partial baths, vitamin B1/B6 and placebo.
Included were patients of the Tumor Biology Center and out-patients with symptoms of a distal symmetrical polyneuropathy developed after a completed chemotherapy that were subjectively related to the therapy, who had no other treatment of the polyneuropathy with drugs or else during the last four weeks. The treatment was applied according to the protocol as electrostimulation-acupuncture to the upper and/or lower limbs or as a hydroelectric bath, given 2–3×weekly over 3 weeks (6–9 treatments) respectively, or as a daily dose of combination of vitamin B1/B6 or of placebo, given over 21 days per os respectively.

Main target parameters were the subjective complaints on the basis of a polyneuropathy described by the patients by means of a numerical rating scale. As additional goals, possible changes in the neurological examination in accordance with electroneurography and classification (CTC criteria) as well as the quality of life estimated through EORTC QLQ-C30 were evaluated.

The data were collected at three different times: before the start of the treatment, immediately after the end of the treatment and twelve weeks after the start of the treatment. The recruitment will be finished in December 2002, data will be un-blinded and evaluated immediately.

2.7.5 Cancer Related Fatigue: A New Challenge for Treatment and Rehabilitation

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A large number of cancer patients experience fatigue during the course of disease either as a side effect of treatment or as a disease symptom. In some cases fatigue can continue for many years once treatment has ceased. Fatigue as a common symptom can seriously impair the patients quality of life and has various implications for the patient’s adaptation and social integration. Studies in epidemiology show overall prevalence rates ranging from 50–96%. Although there has been a lot of active research within the last decade, a comprehensive theory explaining the different phenomena of fatigue is still lacking. There are numerous factors discussed on the causes of fatigue including medical conditions, biochemical or pathophysiological factors or psychological factors. In the past few years, fatigue has been increasingly taken into consideration and various measurement instruments have been developed. In the recent scientific discussion the concept of fatigue is based on a multi-dimensional approach focusing on physical, emotional and cognitive aspects. Studies on psychological factors are focusing on the correlation between fatigue and depression as well as anxiety. Fatigue is a common symptom of depression and has been associated with anxiety and depression. Nevertheless the interdependence between fatigue and depression or anxiety is not yet completely explained. There is also some empirical evidence that fatigue may be regarded as a coping strategy in the sense of self-protection or as denial or defense mechanism. There are only a few studies investigating the complexity of interactions between physical and psychological aspects of fatigue. But fatigue is not only affecting the individuals QoL, but has a lot of consequences on health economy as well as the vocational integration. Patients complaining about fatigue show a higher demand rate of physician counseling, private practitioner or other health services. In the same way, they show higher rates of sick leave and loss of work capacity. Therefore the significance of the fatigue problem in rehabilitation and aftercare is evident. On this background the presentation is reviewing the recent scientific results and focusing on the implications for assessment and intervention strategies in rehabilitation.

2.7.6 Nursing in Oncology: Expanding Roles of the Nurses in the German Language

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Wir alle wissen, dass es in der Bevölkerung einen großen Beratungsbedarf zu Gesundheitsfragen gibt. Mittlerweile werden ca. 15.000 Internetseiten zum Thema Gesundheit angeboten, von denen, nach Schätzung der Ärztlichen Zentralstelle für Qualitätssicherung, ein knappes Drittel seriös sind.

Aufgrund dieses Wissens und den vielen Rückmeldungen der Pflegenden aus ihrem Alltag, hatte sich die Universitäts-Frauenklinik Freiburg vor ca. 2 Jahren entschlossen, in ihrem Hause einen Ort zu schaffen, an welchem Frauen jeden Alters Beratung und Unterstützung zu Themen der Frauengesundheit angeboten werden. Aus dieser Idee wurde »Das Gesundheitsprogramm« der Frauenklinik entwickelt, welches sich in 3 Bereiche gliedert, bzw. 3 Gruppen von Frauen ansprechen soll,
1. für Frauen in gesundheitlichen Krisen,
2. für Frauen in den Wechseljahren,
3. »Die Elternschule«
   – für Frauen und Paare vor, während und nach der Schwangerschaft.

Besonders bei den Angeboten für Frauen in gesundheitlichen Krisen, zu welchen die onkologisch erkrankten Frauen gehören, gibt es viel Entwicklungsbedarf. Hier gilt es einerseits, die verschiedenen Angebote zu bündeln, andererseits den individuellen Bedürfnissen der tumorerkrankten Frauen gerecht zu werden.

Die positiven Rückmeldungen aus unserem Gesundheitsprogramm geben uns die Sicherheit, dass wir uns auf dem richtigen Weg befinden und dass es vorteilhaft war, diese speziellen Angebote für Frauen zu konzipieren.
3.1.2 Die SZT-Assistentin in der Pädiatrie: Ein neues pflegerisches Handlungsfeld?
Wider S.
Station Pfaundler, Klinik für pädiatrische Hämatologie und Onkologie Freiburg


Im pflegerischen Bereich sind die Arbeitsschwerpunkte die Aufklärungsgespräche mit Eltern und Patienten bezüglich der Pflege, Hygiene und Ernährung vor und während der SZT und die Einarbeitung von neuen Mitarbeitern in die spezielle Pflege der SZT. In jährlichen Abständen werden die speziellen Pflegestandards überarbeitet und aktualisiert. Um die Änderung an das Pflegeteam weiterzugeben und um im Austausch mit diesem zu bleiben finden regelmäßige Fortbildungen statt.


3.1.3 Fatigue – Ein pflegerelevantes Thema für die pädiatrische Onkologie?
Bächle B.
Station Pfaundler, Klinik für pädiatrische Hämatologie und Onkologie Freiburg

Schon seit Jahren wird das Symptom Fatigue bei krebskranken Erwachsenen beschrieben und auch erforscht. Fatigue ist ein Problem, welches von den Patienten als sehr belastend und die Lebensqualität einschränkend erlebt wird. In der pädiatrischen Onkologie findet dieses Phänomen bisher kaum Aufmerksamkeit, was auch für unsere Station zutrifft. Dies veranlasste das Pflegeteam der onkologischen Kinderstation, des Zentrums für Kinderheilkunde und Jugendmedizin der Universitätsklinik Freiburg, dazu eine Befragung bei Patienten und Eltern durchzuführen. Wir wollten herausfinden, ob es Fatigue in der Kinderonkologie gibt und ob es für die Pflege relevant ist?


3.1.4 Depression – ein wenig beachtetes Phänomen
Mann A., Müller-Fröhlich C.
BNS, Studium der Pflegewissenschaft, Universität Basel


Ein abschließender Ausblick beinhaltet Konsequenzen für die Pflege.

3.1.5 Körperbildstörungen bei gynäkologischen Patientinnen
Held B.
Station Kaltenbach, Universitäts-Frauenklinik Freiburg


Durch die ständigen Entwicklungen und Verbesserungen der chirurgischen und medizinischen Methoden wurden grosse Fortschritte in der Krebstherapie erzielt. Doch was nützt dies, wenn die Patientinnen

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ihn Ausschen, die Veränderungen ihres Körperbilds nicht akzeptieren, nicht damit leben können?

Pflegenden haben bei der Bewältigung von Körperbildstörungen ihrer Patienten eine wichtige Funktion. Durch ihren intensiven und engen, meist sehr körpernahen Kontakt bei der täglichen Arbeit haben sie einen grossen Einfluss auf die Patientinnen.

Die allgemeine und spezielle Pflege von onkologischen Patientinnen stellt oft hohe Anforderungen an das Pflegepersonal. Für eine ganzheitliche Versorgung ist zudem eine Sensibilität für Körperbildprobleme, Einfühlungsvermögen, fachliches Wissen und Können erforderlich.

3.1.6 Betreuung Angehöriger

Nägele M.
Station Tannhauser, Medizinische Universitätsklinik Freiburg


3.1.7 Palliative Care – Begriffsbestimmung, Pflegerische Gesichtspunkte und Versorgungssituation

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3.2 Hematologic Neoplasia

3.2.1 The Actual World Health Organization (WHO) Classification of Tumors of the Haematopoietic and Lymphoid Tissues: Histopathological and Epidemiological Aspects

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As an actual project, the WHO edits a series entitled ‘World Health Organization Classification of Tumors which is the work of pathologists, clinicians and geneticists from many countries. The third volume ‘Pathology and Genetics of Tumors of the Haematopoietic and Lymphoid Tissues was published in 2001. This volume focuses on disease entities which are clearly characterized by pathological, molecular genetic and clinical features. Moreover, epidemiology, age and sex distribution, sites of involvement, precursor lesions, prognosis and predictive factors are considered. The classification is based on the consensus of the ‘Revised European American Classification of Lymphoid Neoplasms’ which recognized precursor and mature neoplasms of B, T and natural killer cell origin and Hodgkin’s lymphoma. In addition, the WHO classification covers myeloid neoplasms, i.e. chronic myeloproliferative and myelodysplastic syndromes, mixed myelodysplastic/myeloproliferative syndromes, acute myeloid leukemias including myelosarcoma, immunodeficiency associated lymphoproliferative disorders, the rare true histiocytic and dendritic cell neoplasms and different mast cell disorders. Many types of the myeloid disease categories are defined according to the French-American-British classification. However, there are important new aspects. According to the new WHO classification, a basic requisite for the diagnosis of most forms of AML is the presence of at least 20% of blasts in the bone marrow which represents a reduction of 10%. Moreover, the association of some recurrent chromosome abnormalities, mainly balanced translocations, with morphologic and prognostic categories of AML are now taken into consideration. Other groups include AML with multilineage dysplasia and AML, therapy related. This overview focuses on the differences between the well established categories of lymphomas/leukemias and the new classification system. The designations ‘overlap syndromes’ and ‘unclassifiable diseases’ that fail to meet the criteria of any of the specific entities are discussed in detail.
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3.2.2 Diagnostic Standards for Hematologic Neoplasms

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While the classification of hematologic malignancies has undergone profound changes during the last 10 years, traditional morphologic and immunophenotypic analysis of cytological specimens still provide sufficient information to achieve an exact and rapid diagnosis in the vast majority of cases of acute and chronic leukemias. In acute leukemia the myeloid lineage (AML) can be defined by cytochemical demonstration of myeloperoxidase activity in the blast population in > 90% of all cases. Immunophenotyping with detection of myeloid differentiation antigens (CD13,33,15,65,117 and myeloperoxidase) identifies cytochemically peroxidase negative AML. Immunophenotypic definition and subclassification of acute leukemias of the lymphatic lineage is required to assign the patients to the appropriate therapeutic strategies. Non-Hodgkin’s lymphomas such as CLL or mantle cell lymphoma likewise are characterized by a typical morphology and a specific immunophenotype.

Nevertheless there is continuously growing information of typical genetic aberrations in the respective diseases. The ‘World Health Organization Classification of tumors of hematopoietic and lymphoid tissues’ has integrated the aberrant genotype of the respective diseases in addition to clinical presentation, morphology and immunophenotype, and thus serves as an internationally accepted classification tool that will help to facilitate the communication and understanding and the efficient treatment of these diseases.

3.2.3 Molecular Diagnostics in Hematological Neoplasias

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Most cases of hematologic neoplasias can be diagnosed on the basis of clinical history and microscopic evaluation of blood and bone marrow smears and bone marrow or tissue histology. However, the recently established tools of molecular pathology can provide proof that lymphoid cell proliferations are clonal T lymphocytes or B lymphocytes. These methods aid in the diagnosis of morphologically suspicious cases of probable lymphoma, they help to determine if two morphologically distinct lymphomas occurring in one patient are clonally related and they allow an earlier accurate diagnosis of low grade lymphomas such as CLL. We present the diagnostic principles of clonality studies that nowdays consist of PCR-amplification of rearranged T-cell receptor gamma and immunoglobulin heavy and light chain-genes. The PCR products are analyzed by heteroduplex analysis and gene-scanning since both methods generate results that greatly improve the interpretation of morphological assessments. Sequencing of the rearranged immunoglobulin heavy chain genes allows to demonstrate the presence or absence of somatic mutations which has significant prognostic implications in CLL. Besides the studies of clonality, molecular diagnostics can demonstrate the presence of certain chromosomal translocations such as t(14;18) and t(11;14) that aid in the definitive histological diagnosis of follicular and mantle cell lymphomas.

In contrast to the methods that depend on the PCR analysis of DNA extracted from fresh, frozen or paraffin-embedded material, the presence of gene fusions can be demonstrated by the isolation of RNA from fresh and frozen tissue samples. The RNA is transcribed into cDNA and amplified using RT-PCR to detect the BCR/ABL translocation in patients with suspected CML as a diagnostic tool to differentiate CML from reactive leukocytoses and from other myeloproliferative diseases. Moreover, the molecular detection of the BCR/ABL translocation is useful to follow-up CML patients after therapy. Various other gene fusions can be detected by RT-PCR in patients with different subtypes of AML. In BCR/ABL-negative female patients with histologically suspected myeloproliferative diseases or MDS, clonality of hematopoiesis can be investigated using the HUMARA assay, providing clinically useful information in selected patients. Thus, molecular diagnostics provide tools that improve the diagnostic confidence in the diagnosis of hematological neoplasias, allow early diagnosis, are useful to detect minimal residual disease and become increasingly important to determine prognosis and a more differentiated therapies.

3.2.4 Myelodysplastic Syndrome (MDS) in Children and Adolescents

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MDS is a clonal disorder of an aging stem cell which has accumulated a variety of genetic alterations during decades of life. Consequently, MDS and myelodysplasia-related AML (MDR-AML) are common forms of hematologic malignancies among the elderly. In childhood, MDS has an annual age specific incidence rate estimated at only 1.3 per million per year (excluding Down Syndrome and juvenile myelomonocytic leukemia). It accounts for about 4% of hematopoietic neoplasia in this age group. Why have these few cases of MDS in children gained increasing attention recently? There are three principal reasons why MDS in childhood needs be understood. First, MDS often develops in children with known predisposing genetic conditions like inherited bone marrow failure disorders. Studying the mechanism of leukemogenesis in these individuals with well-described genetic defects will gain insight into the pathophysiology of MDS in the elderly. It is reasonable to assume that every child – including the otherwise healthy with so-called ‘primary’ MDS – has some sort of underlying genetic defect predisposing to MDS at young age. Second, stem cell transplantation (SCT), currently the only curative therapy for MDS, can successfully be applied in young individuals, but is generally precluded for the elderly. In multi-center clinical trials of SCT in children and adolescents the importance of pre-transplant cytoreduction, conditioning regimen or graft-versus leukemia (GVL) effect can be studied for the different cytogenetic subgroups. Results will give some important insight for treatment efforts of adult patients. Third, SCT can cure about half the children with MDS and MDR-AML indicating that MDS is no longer a fatal disorder. In summary, recent advances in understanding the pathophysiology of MDS and the current improvements in therapy have changed our approach to patients with MDS and MDR-AML.
Acute Leukemias and Myelodysplasia in the Adult: No Reason for Therapeutic Nihilism

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Before the advent of combination chemotherapy (given in repeated courses), the cure rate of acute leukemia was virtually nil. A further increase in the long-term cure was significantly associated with the possibility of allogeneic bone marrow and later peripheral blood stem cell transplantsations. Thus the majority of patients below the age of 60–65 years with acute myeloid leukemia (AML) is now offered allo- geneic transplantation, and a subgroup of patients with acute lymphoid leukemia (ALL) receives the same treatment option in first complete remission (e.g. high-risk ALL with Philadelphia chromosome or initial induction failure). Acute promyelocytic leukemia (with translocation 15:17) is frequently cured solely with repeated chemotherapy (in several protocols without cytarabine, AraC), during induction in combination with all-trans retinoic acid (ATRA) to induce differentiation. Another cytogenetic subgroup of AML, the so-called CBF leukemias (translocation 8:21, inversion 16) are not routinely allo-transplanted in first complete remission, after a study had shown a high cure rate through high-dose Ara-C [1]. In low-risk MDS patients (no blast excess and normal karyotype, or cytogenetic abnormalities without involvement of chromosome 7 or without complex abnormalities) who are mostly > 60 years of age, anemia is currently treated symptomatically with transfusions and prophylaxis of iron overload, or a trial of recombinant erythropoetin (EPO) is given (rarely effective if the intrinsic EPO levels are very high). Growth factors alleviating the neutropenia of low-risk MDS are reliably effective for transient increase of neutrophils e.g. before surgery or during acute infection, and a remarkable synergism has been described for the combination of Epo and granulocyte-stimulating factor (G-CSF) upon the erythroid lineage [2]. Several new compounds have entered the clinical arena that show response rates in MDS exceeding the 10–20% response rate that spuriously has occurred with multiple different compounds in the past. For instance, ATRA alleviates anemia of the Sd-syndrome in a substantial number of patients, immunosuppressive treatment analogous to that of aplastic anemia improves cytopenias of hypoplastic MDS, thalidomide has activity on several lines in MDS [3], and low-dose melphalan is able to induce responses including complete remissions in patients with MDS with excess blasts and a hypo- or normal cellular marrow [4]. So far, two azanucleosides inhibiting DNA methyltransferases have also resulted in responses including complete remissions, albeit transient, in different types of MDS including high-risk MDS (blast excess, poor-risk karyotype, [5]). With the lowering of the cut-off for the definition of acute myeloid leukemia to > 20% bone marrow blasts, the same options as for AML now apply for patients with myelodysplasia with excess of blasts, for instance after an initial trial with one of the non-curative outpatient regimen mentioned above. Allogeneic transplantation of patients with high-risk MDS and AML using a reduced-intensity conditioning regimen offers a less toxic pre-treatment and a stronger immunologic effect of the graft, allowing for the ‘graft versus leukemia effect’. This option is particularly interesting in patients in the age group between 60 and 70 years of biological age [6].


Radiation of Malignant Lymphomas – a Change in Therapeutic Paradigm

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Since a long time malignant lymphomas are considered to be radiosensitive tumors. Until app. 35 years ago, different sites of lymphomas were treated with small beam – fields, extended on the tumor-manifestation (today one could speak of ‘involved field irradiation’). In the 50th there was no relevant combination of chemotherapeutic agents available. In the retrospective analysis of a typical ‘pa- tient-career’ of that time the summary of the radiation-fields is the so called ‘total-nodal irradiation’.

An important step in the cure of patients with malignant lymphomas was the extended-field irradiation. Starting in the late 60th it was based on the knowledge that Hodgkin’s disease is from the very beginning a systemic disease of the lymphatic system and therefore the treatment of small volumes of this disease is insufficient. The knew radiation technique allowed in the future long-term follow-up studies for the combination of chemo- and radiotherapy. In the meantime new chemotherapeutic drugs were developed for new combinations.

The recommended dose for the treatment of lymphomas could be reduced significantly and the toxicity of combined modality treatment was reduced.

Today we prove in current studies the long-term toxicity of combined chemo- and radiotherapy. The principle of the therapy is: aggressive chemotherapy followed by reduced dose of locally high potent radiotherapy of the bulky tumor or its remainder after chemotherapy. Extended radiotherapy using large fields is rarely used, one could say, that radiation of malignant lymphomas now goes back to its “roots” in the 50th, but today the use and the dosage of radiation is more precisely grace to modern diagnostic tools and it has to be delivered very precisely if we want to avoid side effects and late sequelae.

High Grade Non-Hodgkin’s Lymphoma: Risk Adapted Therapies

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Patients with non-Hodgkin’s lymphoma (NHL) are treated according to histologic subtype. High grade NHL includes a heterogeneous group of NHL subtypes. Presently the different lymphoma entities are classified according to the unifying WHO classification, that has been developed from the Kiel and REAL, as well as working classifications. Apart from histologic subtype several factors have been identified as independent risk (RF) for relapse and inferior survival after chemotherapy as Ann Arbor stage III/IV, LDH > normal, Karnofsky Index < 80%, age > 60 years, and > 1 extranodal manifestation. The first three RF show independent relevance in the age adjusted international prognostic Index (aa IPI) for patients < 60 years and whereas patients with 0 RF have a 5-year probability of survival of > 80%, this is decreased to about 20% in patients with 3 RF. Several groups therefore presently try to improve survival by increasing therapy intensity including high dose chemotherapy and autologous stem cell transplantation in patients with 2 or 3 RF according to aaIPI. In limited stage (I, II) non bulky high grade NHL long term survival is equivalent (or even better in elderly patients) in patients treated with 4 to 68 courses of CHOP compared to abbreviated chemotherapy plus in-
volved field radiotherapy. Shortening of the interval between CHOP cycles from 3 to 2 weeks seems to increase disease free survival as well as the addition of anti-B cell antibodies (Rituximab). Phase 2 trials suggest that patients with 2/3 RF (aaIPI) benefit from additional high dose chemotherapy in first remission. Autologous stem cell transplantation is standard therapy for patients with chemosensitive relapse and allogeneic transplantation may further contribute to cure in certain high risk patients due to the immunotherapeutic active graft-versus-lymphoma effect.

3.2.8 Follicular Lymphomas (FCL/MCL): When to Treat – New Immunotherapeutic Approaches

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Follicular lymphoma (centroblastic-centrocytic lymphoma according to the Kiel classification) is characterized by an indolent course with a median survival of 6–12 years. However, stratification by risk factors (RF) according to the International Prognostic Index (IPI, RF: Karnofsky score < 80%/ECOG < 1; Stage III/IV; LDH > normal; age > 60 y; > 1 extranodal site) differentiates the prognosis with a 5-year survival probability from 85% in the case of 0/1 RF, 60% with 2/3 RF, and only 10% with 4/5 RF. In clinical stage I–II, extended field radiotherapy with curative intent is considered standard of care. However, recent retrospective data from Stanford University show an excellent prognosis with estimated survival probabilities of 97% at 5 years and 85% at 10 years also when treatment is deferred to clinical progression or to development of clinical symptoms. In clinical stage III–IV, an indication of therapy exists only when B symptoms, cytopenias, compressions by lymphomatous masses or other clinical problems are present. Depending on age, progression kinetics, and comcomitant illnesses, various therapies from chlorambucil to combination chemotherapies such as CHOP may be used, which will achieve partial remissions in the majority of patients, but rather rarely complete remissions. The combination CHOP + rituximab has shown particularly promising activity in phase II studies; an improvement of overall survival has not been documented. The duration of remission after CHOP is significantly improved by autologous stem cell transplantation in comparison to interferon-alpha; the influence on overall survival in this setting is hitherto also unknown. In clinical relapse, a randomized trial has shown a significant survival advantage for autologous stem cell transplantation. Active immunotherapy concepts are in clinical trials. For unfavorable clinical courses, an allogeneic stem cell transplantation represents the ultima ratio of therapy.

The same overall principles apply to the therapy of mantle cell lymphoma. In clinical relapse, the combination of FCM + rituximab has better activity than FCM alone. The value of autologous stem cell transplantation is currently being assessed in several clinical trials. In the case of rapid clinical progression or modest response to standard chemotherapy, the particularly unfavorable prognosis of this entity with median survival of appr. 3 years must be taken into consideration. Therefore, an allogeneic stem cell transplantation should always be considered early on for patients with mantle cell lymphoma in appropriate age and overall clinical status, and should be performed expediently when an unfavorable course becomes apparent.

3.2.9 Plasma Cell Neoplasms – New Developments in Diagnosis and Therapy

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Plasma cell neoplasms are characterized by the expansion of immunoglobulin secreting, terminally differentiated, end-stage B-cells. The Monoclonal Gammapathy of Undetermined Significance (MGUS) is defined by the presence solely of a monoclonal paraprotein (M-Spike) in the serum and requires clinical follow-up, since up to 30% of these patients may eventually develop multiple myeloma. On the other end of the spectrum there is overt multiple myeloma, a bone marrow based, multifocal plasma cell neoplasm characterized by serum or urinary paraprotein, skeletal destruction and bone pain due to osteolytic lesions, hypercalcemia and anemia. AL amyloidosis, a much rarer but nevertheless grave manifestation is the deposition of abnormal immunoglobulin chains in tissues, leading to limiting dysfunction of affected organs, especially the heart and gut.

The use of FISH technology to the malignant plasma cells has shown that multiple myeloma is associated with a profound genetic instability and genetically aberrant findings in virtually every case of multiple myeloma. The partial or complete deletion of the short arm of chromosome 13 (typically ‘del 13q14’) occurs in up to 50% of newly diagnosed multiple myeloma cases and has been identified as the most important single unfavorable prognostic factor.

The therapeutic tools have been expanded in the past 15 years: high dose chemotherapy with autologous stem cell transplantation (ASCT) has been increasingly used. While the use of ASCT as opposed to conventional melphalan based therapy has shown a significant prolongation of disease free survival in prospective randomized trials, up to now there are insufficient data to prove an extension of overall survival by this approach. Because of the low transplant associated morbidity and mortality (< 2%) the use of ASCT is considered a standard indication for suited patients (good performance status, age< 70 years) in patients with stage II/III disease. In patients not eligible for this therapy, the alexanian protocol with melphalan and prednisone remains the standard for induction chemotherapy.

Thalidomide used as a single agent (100–800mg/day) or in combination with dexamethasone (e.g. 40 mg day 1–4 q28 days) has shown activity even for patients with advanced disease after failure of prior chemotherapy with response rates of 25–63% and a median response duration of several months. For patients with symptomatic bone disease supportive measures include the continuous use of intravenous bisphosphonates, which have been shown to significantly reduce skeletal complications and bone pain.

Longtime remissions from multiple myeloma have mainly be observed after allogeneic stem cell transplantation. Since transplant related morbidity and mortality has been greatly reduced within the last 5 years in this setting, the therapeutic potential of allogeneic stem cell transplantation is currently evaluated in newly diagnosed patients with advanced disease and aged < 60 years in prospective trials as compared to autologous transplantation as the standard treatment. Application of ASCT in patients with AL amyloidosis for the first time has demonstrated some therapeutic benefit in this otherwise relentless disease. However, treatment associated complications are higher as compared to multiple myeloma patients, probably as a consequence of systemic impairment of the vasculature and tissues due to the amyloid deposits. Therefore it becomes more and more important to early identify these patients and to refer them to hematology centers in order to be able to offer these new therapeutic strategies.
3.2.10 Chronic Lymphocytic Leukemia (CLL): New Prognostic Markers and Therapeutic Options

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B-cell Chronic Lymphocytic Leukemia (CLL) is characterized by the relentless accumulation of mature, incompetent B lymphocytes. Despite a common immunophenotype of the leukemia cells and similarities in clinical presentation, the clinical course in individual patients shows a broad variety. Therefore, efforts have been made to identify CLL patients at high risk for progression early in the course of the disease. Clinical staging according to the Rai- and Binet-classifications are routinely used for risk assessment and therapeutic decisions. In addition, cytogenetics and V(H) mutation status have recently been demonstrated to be related to the prognosis in CLL patients. Genomic aberrations are detected in over 80% of CLL cases by fluorescence in situ hybridization (FISH). 11q deletion is associated with marked lymphadenopathy and rapid disease progression. 17p deletion predicts for treatment failure with alkylating agents, as well as fludarabine and short survival times. CLL cases with un-mutated V(H) show more rapid disease progression and shorter survival times. Whether CD38 expression can serve as a surrogate marker for V(H) mutation status is currently discussed. These new prognostic markers may help to identify in particularly young CLL patients at high risk for progression and may justify a more aggressive treatment in such patients. Alkylating agents such as chlorambucil have been the gold standard for treatment of CLL patients over the last decades. Monoclonal antibodies directed to B cell surface molecules have recently been developed as new therapeutic tool in B cell neoplasias. Anti-CD20 mAbs (Rituximab) and anti-CD22 mAbs (alentsumab/Campath-1H) have been or are currently evaluated in clinical trials in CLL. Recent trial using Rituximab alone or in combination with fludarabine and endoxane demonstrated clinical activity in pretreated patients with B-CLL and tolerable toxicity. Alectumumab was effective in producing responses in about one-third of patients who had failed to respond previously to chemotherapy, including fludarabine and has been shown to display powerful effects in clearing malignant CD52-bearing cells from the blood and bone marrow. However, immunosuppressive effects of this antibody may increase the risk for opportunistic infections.

3.2.11 Treatment for Primary CNS Lymphoma (PCNSL)

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Primary NHL of the CNS (PCNSL) carry a poor prognosis despite initial response to steroids and radiotherapy. Addition of methotrexate to radiotherapy has improved the prognosis of patients with PCNSL, but a significant proportion of patients are still not cured. The combination of radiotherapy with systemic and intrathecal chemotherapy leads to a high proportion of late neurotoxicity especially in patients older then 60 years. The use of high-dose lipophilic blood-brain-barrier-penetrating agents (BCNU, Thiotepa) in addition to maximum doses of water-soluble agents (MTX, AraC) is a novel approach in the treatment of PCNSL. To improve relapse free survival in patients with PCNSL and to reduce neurotoxicity we initiated a multicenter phase II study with early dose intensified chemotherapy and PBSCT followed by hyperfractionated whole-brain radiation for patients aged <65 years. To reduce the risk of delayed neurotoxicity, intrathecal chemotherapy was completely avoided in this protocol and chemotherapy was administered before hypofractionated radiotherapy. Induction treatment included three repetitive cycles of high-dose MTX (8g/m²), AraC (2x 3g/m²) and Thiotepa (40 mg/m²) followed by r-Г-CSF were used for stem-cell mobilization. The conditioning regimen included BCNU (400mg/m²) and Thiotepa (2×5 mg/kg BW) prior PBSCT. Additional hyperfractionated whole-brain radiotherapy (45 Gy in CR, 50 Gy in PR, 2×1 Gy/day) was administered as consolidation. Until now 30 patients were treated within the study. The therapy is very well tolerated with little acute toxicity and with a high rate of complete remissions in patients with PCNSL. Patients older than 65 years were treated with 3×3 g/m² MTX per cycle in combination with Procarbacin and CCNU without radiotherapy, leading to acceptable remission-rates with a low proportion of neurotoxicity. In conclusion sequential systemic application of high-dose differential acting cytostatic agents with consolidating hyperfractionated radiotherapy is well tolerable and results in high remission rates. The abandonment of radiotherapy in older patients leads to a proportion of cured patients without neurotoxicity. Furthermore, the role of consolidating radiotherapy in first remission in addition to high-dose methotrexate is presently evaluated in a randomized trial.

3.2.12 Late Effects after Treatment of Hodgkin’s Disease

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Hodgkin’s Disease is one of the most curable cancers in adult. With new regimes, more than 90% of patients are expected to survive, particularly at the early stages. However, with the recognition of treatment efficacy also has come an appreciation of long-term sequelae. Among this late effects, the induction of second malignant neoplasms represents one of the most feared complication. The most frequently reported secondary malignancy are solid tumors with a frequency of 10–15%, 10 or 15 years after end of therapy. Other observed secondary malignancies are AMLs, MDS and non-Hodgkin’s lymphomas. The risk of second neoplasms depend on treatment associations and patient related factors. Other late effects after treatment of Hodgkin’s Disease are sterility, chronic fatigue syndrome and cardiopulmonary toxicity. The aim of new regimes must be to finding the balance between maximizing cure and minimizing late effects.

3.3 Gynecologic Cancer

3.3.1 Gynecological Cancer Unit: A European Initiative

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During the last decades it was recognized worldwide, that standardized training and centralization of Gynecologic Oncology is mandatory for the improvement in the treatment of patients with gynecological cancer. Twenty to thirty years ago in the USA and later in Australia „Gynecologic Oncology „ was recognized as a subspecialty. This development did not happen in Europe, as the medical systems
Epithelial carcinoma of the ovary is one of the most common gynecologic malignancies (8,000 women per year in Germany) and the fifth most frequent cause of cancer death in women. Approximately 5–10% of ovarian cancers are familial. The most important risk factor for ovarian cancer is a family history of a first-degree relative (mother, daughter, or sister) with the disease. In most families affected with the breast and ovarian cancer syndrome or site-specific ovarian cancer, genetic linkage has been found to the BRCA1 or BRCA2 gene locus. The lifetime risk for developing ovarian cancer in patients harboring germ-line mutations in these genes is substantially increased over the general population. Recent data suggest for patients at increased risk, prophylactic oophorectomy may be considered after the age of 35 if childbearing is complete. A recent retrospective study showed a risk reduction by up to 96%. However, the benefit of prophylactic oophorectomy has not yet been fully established. In Germany, two thirds of the patients are diagnosed in late stages, because ovarian cancer is often asymptomatic in its early stages. Ovarian cancer usually spreads via local shedding into the peritoneal cavity followed by implantation on the peritoneum, and via local invasion of bowel and bladder. The incidence of positive nodes at primary surgery has been reported as high as 24% in patients with stage I disease, 50% in patients with stage II disease, 74% in patients with stage III disease, and 73% in patients with stage IV disease. The resulting impairment of lymphatic drainage of the peritoneum is thought to play a role in development of ascites in ovarian cancer. For prognosis, multivariate analyses suggest that the most important favorable factors include younger age, good performance status, cell type other than mucinous and clear cell, lower stage, well differentiated tumor, smaller disease volume prior to any surgical debulking, absence of ascites, and – most importantly – smaller residual tumor following primary cytoreductive surgery. For patients with stage I disease, the most important prognostic factor is grade, followed by dense adherence and large-volume ascites. Early stages of the disease are curable in a high percentage of patients. Long-term follow-up of sub-optimally debulked stage III and stage IV patients reveals a 5-year survival rate of less than 10% even with platinum-based combination therapy.

For stage I standard treatment option is total abdominal hysterectomy and bilateral salpingo-oophorectomy with omentectomy using a median longitudinal incision. For staging purpose, the undersurface of the diaphragm should be visualized and biopsied, pelvic and abdominal peritoneal biopsies and pelvic and para-aortic lymph node dissection are required and peritoneal washings should be obtained routinely. In selected patients who desire childbearing and who have grade I tumors, unilateral salpingo-oophorectomy may not be associated with high risk of recurrence. If the tumor is grade III, densely adherent, or stage IC, the chance of relapse and subsequent death from ovarian cancer is substantial (up to 20%), and a platinum-containing therapy should be applied. As yet, for stage IA/B GI-II no randomized trial has demonstrated a survival advantage for systemic chemotherapy over watchful waiting. As standard treatment option for stage IC to stage IV surgery should include total abdominal hysterectomy and bilateral salpingo-oophorectomy with omentectomy and debulking of as much gross tumor as can safely be performed. While primary cytoreductive surgery may not correct for biologic characteristics of the tumor, there is considerable evidence that the volume of disease left at the completion of the primary surgical procedure is related to patient survival. At the University Frauenklinik in Freiburg, we have successfully introduced several technical appliances such as ultrasound-based surgery with CUSA, the Argon Beam Coagulation Treatment on vulnerable surfaces (liver, spleen) and the LigaSure™ Vessel Sealing System, to increase the rate of optimally debulked patients. In systemic therapy, the combination of paclitaxel and carboplatin (TP) is the treatment of choice following the data by the American Gynecologic Oncology Group (GOG 111) and a large European-Canadian trial. Median survival was significantly better in the TP arm compared with cyclophosphamide/cisplatin CP (24 months versus 38 months; P=0.001). In the European-Canadian trial carried out in patients with both optimally and sub-optimally debulked tumors the relapse-free and overall survival advantages of TP over CP were confirmed. Newly published data (ICON3, 2002) however question, whether taxanes are required in all patients eligible for first-line chemotherapy. In recurrent cancer, the interval between completion of platinum-based therapy and the relapse as well as the clinical symptoms and the tumor size (>3 cm) determine whether secondary debulking (>12 months after completion of therapy) is of benefit and which agent should be used for systemic second-line therapy (carboplatin/cisplatin, topotecan, liposomal doxorubicin, taxanes, etoposide, gemcitabine, tamoxifen, others). Newly developed therapies to specifically target tumor cells on a molecular level, as being studied at our hospital, may in future help to control tumor progression and allow patients to live with cancer with a preserved good quality of life.
Therefore, it is important to offer advice and medical help. An open setting and the acceptance of the patient’s colloquial language creates a trustful atmosphere. Differences in individual experiences, biographical background, and the cultural context have to be considered. For women and men, sexuality may be of different importance and can change with partner and period of life. It is a rewarding challenge to show cancer patients that communication is better than resignation and that every crisis offers the chance of development as satisfactory sexuality has positive effects on the physical and psychical health of each patient.

3.3.4
Modern Management in Gynecological Oncology: Endometrial Cancer

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Endometrial cancer represents the most frequent malignancy of the female genital tract with an incidence of 24.7/105 women and 11,500 newly diagnosed patients per year in Germany. The median age at the time of diagnosis is 68 years, the 10 year overall survival rate is about 58%. Obesity, early menarche and late menopause are the main epidemiological risk factors, but low parity and estrogen-producing tumors are known to increase the risk also. Uterine bleeding of the postmenopausal patient is the most important symptom of endometrial cancer.

Modern management of this disease includes the efficient diagnostic evaluation of symptomatic patients as well as pre-therapeutic staging (esp. the fractionated curettage), which is essential to identify the extent of disease as well as the individual risk profile. These procedures allow to define the extent of surgical treatment which has to be determined individually for each single patient. In this regard surgical staging and risk adapted lymphadenectomy are important and integrated measures in modern management of endometrial cancer. The stage-dependent surgical procedures reach from abdominal hysterectomy plus adnexitomy to pelvic exenteration. Besides surgical procedures primary and post-operative radiotherapy are still stage-dependent important treatment options.

Modern management of endometrial cancer demands the stage-dependent and risk adapted individualized treatment of patients including surgery, radiation and systemic therapy.

3.3.5
Modern Management in Gynecologic Oncology: Cervical Cancer

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Since the introduction of the PAP smear in 1971, the incidence of cervical cancer in Germany could be reduced from 35.8/100,000 to 12/100,000. However, cervical cancer is still the second most frequent cancer among women worldwide. 60% of the affected women are younger than 60 years. The presence of nodal metastases is the most important prognostic factor for survival in early stage cervical cancer. The five-year disease free survival rate for patients with negative lymph nodes (LNs) is between 88% and 93%, for patients with positive LNs only between 40% and 63%. Patients with stage I disease were reported to have nodal metastases in 15.4%, with stage II in 28.6%, and with stage III disease in 47%. Discrepancies between clinical staging and surgical-pathologic findings occur in about one fourth of the patients. Therefore, pelvic and paraortic LNs should be histologically evaluated prior to each radical surgery. In cases with nodal metastases, a combination of chemotherapy and radiation is performed as it was shown that this treatment approach significantly improves disease-free and overall survival.

Even in patients with advanced disease, the level of positive LNs should be evaluated, as it helps to define the RT field and provides prognostic information. As transperitoneal lymph node dissection was proven to be hazardous for patients who subsequently require radiotherapy, an extraperitoneal lymph node dissection is preferable. In addition to limiting adhesion formation, this provides exposure of the retroperitoneum and pelvic ureter, while having an intact peritoneum to aid in retraction. To minimize morbidity, primary therapy should avoid the routine use of both radical surgery and radiation therapy.

3.3.6
Minimal Invasive Therapy for Patients with Gynecologic Malignancies

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For a long time minimal invasive techniques were considered to only play a role in the staging of gynecologic malignancies. However it could be demonstrated that a laparoscopic lymphadenectomy both pelvic and paraaortic is feasible and adequate. In experienced hands it can achieve the same radicality as by laparotomy. Especially French groups developed transperitoneal and extraperitoneal laparoscopic techniques allowing similar radicality up to the left renal vein as an open procedure.

Stage I Cancer of the Cervix thus can be either operated using an entirely endoscopic technique or utilizing a combination of radical vaginohysterectomy with laparoscopic lymphadenectomy. The advantage of such an approach is seen in a reduced damage to accompanying structures – nerve sparing technique – and an improved visibility due to the magnification allowing improved parametric exposure and resection.

Similarly an abdominal incision may be avoided for a large number of patients with early endometrial cancer (FIGO Stage I) by employing laparoscopic staging and laparoscopic assisted vaginal hysterectomy with bilateral salpingo-oophorectomy. Comparative studies indicate that the laparoscopic approach is associated with shorter hospitalization, faster recovery and an improvement in quality of life. With respect to the coming DRG system it might even be the more economic approach due to the shorter hospitalization.

Prerequisite for these positive results however is extensive experience of the surgeon in endoscopic surgery. Only then extended operating times and compromise in radicality can be avoided. So far the relapse rates after laparoscopic surgery as published by groups with experience in these techniques do not differ from those reported after a conventional approach.

The role laparoscopy will play in ovarian cancer is still to be defined. At the moment there is a place only for patients with very early and limited disease. But in these cases laparoscopy can avoid the need for a staging laparotomy whilst providing the same information by omentum biopsy and lymphadenectomy. However if a second look procedure is necessary for the decision about further therapeutic interventions beginning with laparoscopy may make laparotomy unnecessary in the majority of patients.
Management of vulvar cancer during the last 20 years has developed towards conservative procedures in the therapy of the early stage disease. Women with invasive tumors > 20 mm (T1) are treated by a radical local excision. The lesion should be unifocal and the rest of the vulva healthy. A surgical margin of at least 10 mm should be obtained. If no focus with greater than 1 mm of stromal invasion is present, lymph node dissection may be omitted. Lateral lesions with a depth of invasion > 1 mm may undergo unilateral inguinal-femoral lymphadenectomy. Midline lesions and those involving the labia minora require bilateral groin dissection. In selected cases radical local excision on the primary lesion may also be performed in T2 lesions > 20 mm but should always be combined with a bilateral inguinofemoral lymphadenectomy. Adjunct pelvic and groin irradiation should be given if at least one large node has undergone a timorous change of if there are multiple nodes containing micrometastases. Careful patient selection is necessary to successfully achieve high cure rates, acceptable cosmetic results and psychosexual wellbeing.

3.4 Urological Cancer

3.4.1 Why Men Don’t go for Preventive Health Check-Ups?

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The public is getting more and more aware of the problem of men’s health. Men die about six to seven years earlier than women. The high prevalence of health-risk behaviors such as smoking, heavy drinking, drug abuse in men in comparison to women might be some reasons for that. Complementing this tendency few men are engaged in preventive health behaviors like free preventive health check-ups. This behavior has been described in the literature and by several official health reports world-wide. For example the «Wiener Männergesundheitsbericht 1999» reports that only 9% of men over 20 years are regularly participating in preventive check-ups. Analogous data from the Deutsche Krebshilfe indicate that only about 16% of men claim their free preventive cancer check-up. This data is confirmed by the men’s health’s-study performed by the polling-institute Allensbach. According to their data 25% of men compared to 50% of the women are regularly participating in these examinations.

Reasons for the negative preventive health behavior might be found in a gender role self-concept influenced by genetics, educational and environmental factors.

On the one hand men try to identify themselves with a traditionally male ‘macho’ stereotype, characterized by strength, independence, willingness to take risks. On the other hand data show that men seem to be rather sensitive, anxious and social creatures.

These latter aspects are reflected by data showing that about 50% of the men go to work although feeling sick for reasons of dissimulation, feeling the need to take care of important work and team spirit. The self-concept of being independent, strong, able to cure themselves becomes apparent by the fact that men often help themselves with medication for which no prescription is needed. Even if they go to see their treating physician they often (42%) don’t follow the instructions. When looking for reasons for not going to see the doctor, men often name long waiting time. Additional aspects are fear for bad news and painful examinations.

Another concept might be the lack of an equivalent to the ‘gynecologist for men’. Since women are more or less responsible for contraceptive measures in our society, a great proportion of girls start to go to the doctor in their adolescence. Thereby they loose their fear for consulting doctors including pelvic examinations. This habit of regularly seeing the gynecologist is reinforced in times of pregnancy. A time when a woman is not only responsible for herself but for the child in her. This period is followed by the time of bringing up children, with the mother again being the major care-taker.

All these facts might increase the awareness of health risks in women and the other way round might be another explanation why men aren’t used to and don’t really learn to live according to preventive ideas.

So in conclusion the etiology of male negative preventive health behavior seems to be multi-factorial. Further studies are on the way (personal communication) and will be needed to find out more about the major influences in order to engage men in preventive check-ups.

3.4.2 ‘Prostate Carcinoma Genes’ and Their Role Nowadays

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Family history is an established risk factor for prostate cancer and families demonstrating autosomal dominant or X-linked transmission of susceptibility have been observed. In contrast to mammary or colonic carcinoma, hereditary prostate cancer (HPC) is not due to mutations in a single or a few genes. At least six major susceptibility loci or candidate genes have been discovered by positional cloning strategies, reflecting tremendous genetic heterogeneity of HPC. Nevertheless, as only 5 to 10 percent of prostate cancer cases in the population may arise from major susceptibility genes, other genetic factors, in combination with exogenous risk factors, may be of more significance in prostate cancer etiology. Genetic polymorphisms that may be associated with prostate cancer risk are much more common in the population than are high-penetrance cancer susceptibility genes.

The search for genetic markers for prostate cancer susceptibility has revealed an increasing number of relatively common genetic polymorphisms. Considering putative clinical utility, the most interesting polymorphisms affect the androgen receptor gene, the S alphareductase type II gene, the prostate-specific antigen gene and the vitamin D receptor gene. However, for many of the genetic polymorphisms, associations with prostate cancer risk have been inconsistent across studies.

In summary, it has to be assumed that prostate cancer develops from complex interactions among many genetic and environmental factors over time. Identification of major susceptibility loci, candidate genes and genetic polymorphisms, which are associated with increased prostate cancer risk, improves our knowledge of the prostate cancer, but is of no clinical value today. Consequently, recognition of genetic high-risk prostate cancer individuals is still based on a thorough evaluation of the family history.
3.4.3 Prostate Carcinoma – Primary Prevention: Chemo-Prevention and Diet

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The prostate carcinoma is a typical tumor of the elderly male with high histological prevalence. Among men over 70 years the progression rate is low and it occurs in competition with other causes of death within the elderly population. Out of this reason it seems to be an ideal tumor for chemo-preventive approaches. To reach a positive effect merely the clinical proliferation has to be delayed. The level of awareness today suggests that these preventive measures have to be taken around the age of 40.

When looking at the incidence of prostate carcinoma, disregarding the age, considerable geographical differences show. Autopsy studies though show the same incidence of latent (not clinically apparent) carcinomas in East and West. However, the clinical incidence of prostate carcinomas for instance is 20 times higher among North-American Blacks than among Japanese and 120 times higher compared to Chinese people from Shanghai. If these Japanese people migrate to North America, they are half at risk to get a clinically apparent prostate carcinoma within two generations compared to native North-Americans. So it suggests itself to make dietary factors, besides genetic differences, responsible for the statistical differences.

The data were the starting point for the question about the influence of Asian food on the low incidence of prostate carcinomas. Asian food consists mainly of carbohydrates, the animal proportion of fat and proteins is 10% at most. Numerous studies could show the connection between the high fat portion of our diet and the incidence of clinical prostate carcinomas as well as mamma carcinomas.

In addition, Asian food is rich in plant estrogens. These phyto-estrogens (lignanes, flavonoids and iso-flavonoids) are said to have protective characteristics against cancer. Besides pure phyto-estrogens, an inhibition of 5-alpha-reductase is described, having the effect of reduced dehydrotestosterone activity. Moreover, influences on the aromatase, an inhibition of thyroside-specific kinases, like the topoiso-merases, has been proven. Angiogenesis is also inhibited by numerous phyto-estrogens. What seems even more notable is the clear antioxidative activity as well as the direct anti-tumor effect, that has been shown in numerous animal experiments.

Chemo-preventive substances that have shown an influence on the clinical incidence of the prostate carcinoma are: Selenium in a dose of 100-200 µg/die, diverse carotenoids (vitamin A, ß-carotene), as well as vitamin E in a dose of 400-800 IU/die. Recent data points as well towards the chemo-preventive effects of vitamin D. Furthermore, a lowered incidence of prostate carcinoma has been observed in a small study when applying acetylsalicylic acid in a low dose (100 mg/die), this is possibly valid for the whole group of non-steroidal antirheumatic drugs. In the same way, newer studies are in preparation. The role of 5-alpha-reductase inhibition is being investigated in a big rheumatic drugs. In the same way, newer studies are in preparation. This is possibly valid for the whole group of non-steroidal antirheumatic drugs. In the same way, newer studies are in preparation.

3.4.4 Prostate Carcinoma – Secondary Prevention: PSA Screening

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Since 2001, the prostate carcinoma is the predominant cause of death for the male. Among the group 50-year-old men, the incidence per annum is 20/100,000 and 500/100,000 among the 70-year old men (National Institute of Health, American Cancer Society).

Due to the high frequency, it is essential to establish basic diagnostics to secure early detection of the prostate carcinoma. The introduction of the tumor marker PSA (Prostate Specific Antigen) has improved the detection rate of early tumor stages. Digital rectal examination and transrectal ultra-sonography together with PSA allow an early diagnosis of the prostate carcinoma.

In oncology, PSA is one of the most valuable tumor markers for observing the decline or progression of the disease after radical prostatectomy, radiotherapy or hormonal therapy. Public figures have largely contributed to the awareness of the public about the prostate carcinoma and the acceptance for screening and early detection programs in the United States. Hopefully, Europe will follow this trend, especially because of the high validity of PSA, enabling patients to get a curative therapy in early stages of prostate cancer.

3.4.5 The Influence of Testosterone on the Prostate Carcinoma

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The prostate carcinoma can be brought to involution by withdrawal of the male sexual hormone testosterone by apoptosis. With a response rate of 80% in the case of metastatic carcinoma progression-free time between 18-24 months is to be expected. The fundamental work on this was published by Huggins and Hodges in 1941, who were awarded the Nobel prize for medicine in 1966.

Androgens promote the development of the prostate to become a fully developed organ. In addition, they promote carcinoma growth in different animal models. We also know, that eunuchs or men with a congenital defect in 5-alpha-reductase, never develop a prostate carcinoma. This observation leads in reverse to the question, whether the maintenance of normal testosterone level until the old age is accompanied by a high risk in origination of a prostate carcinoma. However, there is the objection that hypophysectomised patients, getting a testosterone substitute, have a comparatively low incidence in prostate carcinoma.

With increasing age, the level of bio-available testosterone clearly decreases. A 65-year-old man averagely only has a third of the free testosterone level of a 20-year-old man. Can the maintenance of the normal testosterone level even possibly have a protective effect, possibly also by substitution? Hints in literature can be interpreted in this way. In this respect, brothers and sons of patients with prostate carcinoma for instance have lower testosterone levels than the control group [Meikle et al.: 1982]. Patients with testicular atrophy clearly have a lower life expectancy [Daniel: 1998] and a lower grade in differentiation of the carcinoma is accompanied by a lower testosterone level [Hofmann et al.: 2000].

In a comparative examination of patients, who came for preventive reasons, 41% of the men with prostate hyperplasia had a decreased testosterone level, whereas this proportion was at 64% clearly higher among men with prostate carcinoma. Among men under 60 years...
who turned out to have a prostate carcinoma, even 87% showed lowered levels of serum testosterone [Jünnemann: 2001]. For a general conclusion to determine the influence of testosterone on the prostate carcinoma, the data is not sufficient. However, it can be acted upon the assumption that with testosterone and also with testosterone substitution a prostate carcinoma cannot be induced.

3.4.6 Radial Prostatectomy as Treatment Option for Localized Prostate Cancer

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The treatment options for presumably localized prostate cancer include watchful waiting, radiotherapy and radical prostatectomy. Even though no randomized studies, comparing these treatment options, exist, there is an abundance of data supporting the notion, that for men with localized prostate cancer (stagesT1C2a,b) and a life expectancy exceeding 10–15 years, the radical prostatectomy is the therapy of choice. The procedure can be done as RETROPUBLIC, PERINEAL or LAPAROSCOPIC radical prostatectomy. All three procedures have their pros and cons, which will be discussed in detail. All three procedures achieve a removal of the prostate gland, the seminal vesicles and the ampullae of the vasa deferentia. The patient, after a radical prostatectomy, can expect a > 90% continence rate. Furthermore, modern surgical technique applying a nerve sparing surgery, where indicated, can achieve potency rates > 50–60%. A careful selection of patients and appropriate counseling is the key for a successful outcome. This includes considering co-morbidities, that might preclude pursuing a surgical treatment or staging information, consisting of serum PSA, digital rectal exam (DRE) and the Gleason grading of the prostate biopsy, that might suggest extracapsular or lymphatic invasion of the tumor. One of the dilemmas is the proper staging of prostate cancer, since no single imaging modality (MRI or CT) reliably predicts truly localized disease. Therefore, the staging has to rely on serum PSA, DRE and the histology of the prostate biopsy, in conjunction with a pelvic lymphadenectomy and a bone scan, where indicated.

3.4.7 Definitive Radiotherapy of Prostate Cancer

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Prostate cancer belongs biologically to the slowly growing type of solid tumors. High doses of radiotherapy within the target volume are recommended for the treatment of these tumors. The required minimum dose for external beam radiotherapy is 72 Gy. The direct neighboring organs such as urine-bladder, rectum and small bowel have each a limited tolerance to radiation doses, the radiation-tolerance of the bladder is clearly below the tumor cell killing dose needed for the treatment of prostate cancer. In the past the recommended dose for external beam therapy of prostate cancer thus was restricted, the side effects to bladder and/or rectum were tolerable, but the long-term cure-rate was rather poor. Today we can protect the surrounding organs of risk by using conformal 3-D reconstructed radiotherapy based on Ct-scan. Doses of 72-74 Gy in the target-volume are possible with this technique. The not routinely available IMRT (Intensity Modified Radio-Therapy) allows higher treatment-doses, but this method is not for the daily routine and the variations of the prostate in the radiation-fields has to be considered as well as in the normal conformal practice. Doses of 80 Gy or more are possible by using IMRT.

Another procedure for delivering high radiation doses to the prostate and the surrounding margin is the combination of interstitial remote controlled afterloading plus conformal external beam therapy (ebrt). Two times interstitial afterloading is delivered under anesthesia-conditions followed by external beam therapy. The equivalent summary-dose of this combination is about 100 Gy compared to conventional ebrt. Tumors of size ≤T2 or ≤T3a without clinical signs of lymph-node involvement can be treated safely with this method. Since 1992 we have treated about 350 patients with this combination. The afterloading with radioactive seeds is a method only suitable for small tumors within the prostate gland distant from the capsule.

3.4.8 Urinary Incontinence after Prostate Carcinoma Therapy – an Unsolvable Problem?

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While urge incontinence of the elderly man constitutes the most frequent form of urinary incontinence, male stress incontinence occurs overwhelmingly as an effect of operative therapy upon the urogenital tract. Independent from the choice of a surgical way of access, the radical prostatectomy bears the risk of a disorder of the continence apparatus with resulting stress incontinence. Luckily, after several months, most of this disorder disappears. The risk can be diminished clearly by special operation techniques, like apex-near preparation of the urethra, leaving a sufficient length and sparing the extrinsic urethral sphincter.

It is a matter of priority to use all available treatment methods, like physiotherapy of the pelvic floor under specialist instruction and should the occasion arise, additional application of electrostimulation methods. In case of persistent stress incontinence, which also has to be proven by uro-dynamic evaluation, operative procedures have to be taken into consideration. The effect of the minimal invasive transurethral injection procedures with cushioning the urethral part near the sphincter, often clearly decreases after a number of months. The implantation of an artificial sphincter is a great help for a large number of patients. However, a high re-operation rate has to be accepted due to mechanical device problems.

In addition, radiotherapy of the prostate carcinoma (percutaneous, interstitial or combined) can cause urinary incontinence. Mostly this is a form of urge incontinence, improving after termination of radiotherapy.

3.4.9 Impotence Following Therapy of the Prostate Carcinoma – an Unsolvable Problem?

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Impotence or erectile dysfunction is the most frequent side effect occurring in more than 50 % of all cases after a curative treatment of the prostate carcinoma, be it radical operation or radiotherapy. Having an influence on sexuality, it constitutes an enormous problem for many patients. To avoid or minimize this problem a nerve sparing...
operative technique can be applied but is recommended in early stages only. For radiotherapy, an exact planning of the target volume, as well as a fractionated application of the radiation in multiplanar technique is essential. In case of post-operative erectile dysfunction, treatment should start 3 months after the end of therapy. Degenerative changes of the smooth muscles of the cavernous tissue and the autonomic nerves can be expected after this time span. Today, there are numerous and diverse methods for the therapy of erectile dysfunction. These cover oral medication like sildenafil, intraurethral (MUSE) or intracavernous injection of vas-dilative drugs, as well as vacuum devices or the implantation of penile prostheses. Naturally, additionally present risk factors, such as smoking, arterial hypertension, diabetes, hyperlipidemia should be reduced or adequately be treated. With those measures it is possible in most cases to enable patients and their partners a normal sexual life.

3.5 Cancer in Adolescents

3.5.1 Tumors in Adolescents – as Important as Adolescence for Life

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Pediatric malignancies are most commonly observed in infancy. The age specific incidence rate then decreases till early puberty. From puberty onwards it rises steadily during adolescence and early adulthood. In fact, the incidence of cancer among 15–19 year old adolescents is similar to that observed in 1–4 year old toddlers. During the last 25 years, adolescents experienced a smaller increase in survival rates than younger cancer patients. This observation may in part be explained by the fact that adolescents are less likely to receive medical care within controlled clinical trials. It may also be due to the unique distribution of malignant disorders noted during adolescents. Embryonic tumors of early childhood like nephroblastoma, hepatoblastoma, neuroblastoma, retinoblastoma, ependymoma or medulloblastoma do no longer present in this age group. The most common entities of adolescent cancer are Hodgkin’s disease, CNS tumors and germ cell tumors, followed by sarcomas, leukemias and non-Hodgkin lymphoma. Epithelial neoplasia, predominantly thyroid carcinoma and melanoma, account for about 20% of all neoplasia in this age group. Carcinomas of the respiratory or gastrointestinal tract predominating later in life are virtually absent. About two thirds of the malignancies in adolescence can be classified as ‘pediatric type’ and one third as ‘adult type’ cancer. Largely dependent on the initial referral, adolescents may be cared for by pediatric oncologists, adult oncologists or organ specialists. This implies that participation in clinical trials is often by chance, and many adolescents are treated outside multi-center studies. In addition, adolescents with leukemia, Hodgkin’s disease or non-Hodgkin’s lymphoma may be enrolled in the pediatric multi-center trials or in a number of competing adult studies. Unfortunately, there are no data comparing the outcome of patients treated on pediatric versus adult protocols with respect to survival or late effects. The adolescent with cancer generally experiences a number of psychosocial challenges which are special to this age group. Loss of contact to the peer group, the feeling of premature aging and loneliness are among the most common problems. In this session, the unique medical and psychosocial needs of the adolescent with cancer will be discussed in some detail.

3.5.2 Results of Hodgkin’s and Non-Hodgkin’s Lymphoma Studies: Can Therapy be Further Improved?

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Treatment of lymphoma in childhood is an important issue for the pediatric oncologist. Two major subtypes have to be distinguished: Hodgkin’s disease (HD) and Non Hodgkin’s Lymphoma (NHL). Results of therapy are very different according to the histology of lymphoma, and the stage of the disease. In study HD-90, patients were treated with a combined treatment protocol of chemotherapy and radiation according to disease stage. All three treatment groups (TG) received induction chemotherapy with procarbazine, prednisone, adriamycin for girls (OPPA) and two cycles of OEPA (etoposide instead of procarbazine) for boys. Patients of TG 2 and 3 additionally received two or four cycles of COPP (C, cyclophosphamide), respectively. Chemotherapy was followed by radiotherapy to the involved sites (reduced fields if possible) of 25, 25 and 20 Gy in the 3 TG, respectively. For the total group of 578 patients, overall survival (OS) at 5 years is 98% and event-free survival (EFS) 91%. In TG 1, EFS for girls (2 OPPA) is 96%, and for boys (2 OEPA), 94%, in TG 2 and 3 (combined). 92% and 86%, respectively. In the approaches of HD therapy, next to the goal of achieving high survival rates, high priority was given to the reduction of late effects caused by radio- and chemotherapy. The results show that combined modality treatment according to disease stage has very good results and enabled reduced dosages and fields of radiotherapy as well as lowered cumulative total doses of critical cytotoxic agents.

The study NHL-BFM 90 investigated the distribution and prognosis of the different subtypes of NHL in children and adolescents according to histological, cytomorphological and immunological characteristics. Cases with L1 or L2 cytomorphology according to the French-American-British Classification are classified as lymphoblastic lymphoma and those with L3 cytomorphology as Burkitt-Type lymphoma or acute B-cell leukemia (B-ALL) if a histological classification is not available. In 312 cases 40% were classified as Burkitt-type-lymphoma (incl. B-ALL), 22% als lymphoblastic lymphoma, 10% as large cell anaplastic lymphoma (LCAL), 6% as centroblastic lymphoma, only few cases were classified as NHL of other subtypes. 3 patients (1%) suffered from low grade malignant lymphomas, and in 34 patients (10%) the NHL was not further classified. Patients were stratified according to NHL-sub-entities in 3 branches (Non-B-NHL, B-NHL, LCAL) of different treatment modalities. The estimated probability of a 3-year event free survival (pEFS) was 88 +/- 2% for the whole group (follow up 7 to 40 months, median 23 months) while pEFS of different subtypes was: lymphoblastic lymphoma: 91 +/- 4%; Burkitt-type-lymphoma/B-ALL: 90 +/- 2%; centroblastic lymphoma: 94 +/- 6%, LCAL: 88 +/- 6%.

The stratification of treatment modalities in study NHL-BFM 90 according to biological entities provided patients of different NHL-subtypes an equal chance to survive event free.
3.5.3 Sarcomas with Chromosomal Translocations. Requests and Pleas of the Pathologist

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Most of the solid malignancies in children and adolescents are sarcomas, which, in relation to their characteristic histology, reveal specific chromosomal translocations that should be assessed in order to supplement the histomorphological diagnosis. Translocations result in genomic rearrangements and gene-fusion transcripts. The involved genes, which usually encode transcription factors, become impaired or activated by the rearrangement and thus contribute to tumor development. The most important fusion gene is EWS on chromosome 22q12, which in tumors of the Ewing/PNET family is fused with various genes (FLI1 on 11q24, ERG on 1q22, ETV on 7p22 and EAF1 on 17q12). In the desmoplastic small and round cell tumor EWS is rearranged with WT1 on 11p13, in clear cell sarcoma of tendons with ATF1 on 12p13, and in extraskeletal myxoid chondrosarcoma with TEC on 9q22. In the alveolar rhabdomyosarcoma the FKH gene on 13q14 is fused with PAX3 on 2q35 or with PAX7 on 1p36. In synovial sarcomas SYT is rearranged with SSX1 or SSX2 by t(X;18)(p11;q11). Recently a fusion of ETV6 on 12p13 with NTRK3 on 15q25 was reported in infantile fibrosarcoma and in cellular mesoblastic nephroma. The finding was interpreted as evidence of a histogenetic relationship between these two tumor entities.

For RT-PCR molecular analysis fresh or fresh-frozen tumor specimens are required. The surgical procedure, condition and appropriate transport of the specimen should be planned and discussed before the operation, as the necessary molecular probes may not be available in all laboratories. If FISH-analysis is considered, air-dried imprints or thin smears from the fresh cut surface of the tumor are to be prepared by the pathologist immediately after the transfer of the fresh tumor tissue from the surgical theatre to the pathology lab. From the tumor tissue used for the smear a paraffin block should be prepared for documentation of the specific tumor histology at the smear site as tumors may be quite heterogeneous histologically. Similarly, tumor specimens designed for deep freezing in liquid nitrogen and storage at -70°C are to be excised from the fresh tumor by the pathologist, who is going to assess the surgical margins later. In order to enable the pathologist to come to a complete gross and microscopic diagnosis, including localization, size and classification of the tumor (ICD-number), grading, TNM staging and state of resection (R), several additional clinical information is essential. Radiological images (X-rays, CT, MRT) are mandatory in case of bone tumors. Larger tumors should be marked for orientation and for sites of specific interest in relation to neighboring anatomical structures. Gross and histological evaluation of the therapeutic response in a neoadjuvant situation poses another problem for the pathologist. For bone tumors Salzer-Kuntschik introduced a rather time-consuming procedure, by which the remaining vital sarcoma tissues are expressed in per cent of the cut surface along the largest tumor diameter. This procedure is reasonable, since the original size of the tumor is still discernable as the bony edges of the osteolytic cavity are preserved after therapy. In soft tissue sarcomas, however, the original size of the tumor can no longer be determined in the posttherapeutic surgical specimen because the tumor tissues that were necrotized during therapy will become partly dissolved and partly replaced by granulation and scar tissues. If the therapeutic measures were effective, the tumor size and volume will be reduced. Consequently the percent area of vital tumor can only be related to the residual necrotic and scarred areas present in the histological sections and not to the original tumor diameter, which means that the determined %-values of vital tumor tissues are to high and not representative in soft tissue sarcomas.

3.5.4 High-Dose Chemotherapy or Maintenance Therapy? – Treatment Strategies for Sarcomas

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Adolescents have an increased incidence for osteosarcoma and Ewing’s sarcoma as compared to other age groups. The treatment for both tumors is based on the neoadjuvant concept. This means the application of systemic chemotherapy in front of local therapy, which then is followed again by systemic chemotherapy. The advantage of preoperative chemotherapy is not only that it facilitates local therapy by decreasing tumor size, but also that it gives the opportunity to evaluate in vivo chemosensitivity of the tumor. For both diseases the degree of tumor necrosis in the operative specimen has become the most valuable prognostic factor. In patients with Ewing’s sarcoma, whose tumor only show a minor response to chemotherapy, the value of high dose chemotheraphy with stem cell rescue is currently being tested in a prospective randomized study. Whereas in younger children rhabdomyosarcoma is the most common soft tissue sarcoma, in adolescents it only accounts for 25% of tumors. While rhabdomyosarcoma and synovial sarcoma are chemosensitive, other soft tissue sarcomas such as liposarcoma and malignant nerve sheet tumors are not or only poorly chemosensitive. In the latter group, surgery is the treatment of choice. In metastatic rhabdomyosarcoma high dose chemotheraphy with autologous stem cell rescue has not proved to be superior to conventional chemotherapy. Currently, the efficacy of the topomerase 1-inhibitor topotecan and of maintenance chemotherapy is evaluated in this patient group.

3.5.5 Radical Resection and/or Preservation of Function?
Special Issues in Surgical Therapy of Soft Tissue and Ewing Sarcomas

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Sarcomas are rare tumors – except in children. Whereas this kind of malignancies represents about 1% of tumors in adults, the rate is as high as 15% in children and adolescents. A further difference is characteristic: sarcomas tend to metastasize later than carcinomas. Nevertheless, this remains a problem due to the often late diagnosis of the primary tumor. Furthermore, the risk of local recurrence is high. Intense investigation is under way to identify the factors determining the risk of metastasis or local relapse. The first step of dealing with this entity of tumors is important already: diagnosis has to be achieved not by a ‘normal’ surgical way of gaining biopsies, and a variety of pathological investigations are performed. Many of these tumors are characterized by genetic aberrations or specific cytogenetic findings most of which are more significant for the diagnosis than light microscopy. Thus it is mandatory that the biopsy be gained in a correct way: either as an incisional biopsy or as complete removal of a small tumor (excisional biopsy); it is taken to investigations as native specimen. In any case already this procedure has to be planned so that this incision and drainage can be completely resected by the
definitive operation. Depending on the type of tumor, its stage, localization, metastases, and resectability, a decision has to be made concerning neoadjuvant therapy. The operation is part of a multidisciplinary concept. The goal of surgical therapy is the complete removal of the tumor including a sufficient border of healthy tissue around it. Various kinds of extensity can be used:

1. intralesional resection (in case of involvement of vital structures)
2. marginal resection (complete excision without a satisfying layer of normal tissue)
3. wide excision (complete removal of the tumor including an oncologically safe layer of healthy tissue at any area of the surface of the specimen)
4. compartment resection (excision of a whole compartment of a region of the body)
5. multivisceral resection (tumor removal with resection of various adhering organs en bloc).

The first two procedures must be seen as palliative. In the other three kinds of operation a systematic lymph node dissection has to be performed as part of a correct oncologic surgical procedure. In these situations the conflict arises whether to resect a big part of an organ or a great amount of musculature, tendons, vessels, and nerves intending cure of the patient with the effect that a loss of function will result; in contrary, preserving good function will lead to a diminished curability. This dilemma has to be discussed intensely between all physicians involved in the treatment as well as with the parents of the child. In an age of growing understanding this should be explained carefully to the child itself. Especially in case of tumors of the extremities where the treatment will impair the function and by that disturb the quality of life it is mandatory to address the psychosocial aspects. Sarcomas have to be treated in a close cooperation of all oncologically engaged specialties in the frame of a multidisciplinary concept. This leads to significantly improved results.

3.5.6 Treatment Strategies for CNS Tumors in Adolescence

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CNS tumors represent 22% of all cancers diagnosed in childhood (<15 years). In adolescence (15–20 years) they are with 10% the third leading cause of cancer after Non-Hodgkin’s lymphoma (16%) and gonadal tumors (15%). Survival rates have been increasing for all patients, especially for children. This is due to improved diagnostic and therapeutic methods, which have been identified and widely applied in clinical studies.

Surgical interventions mostly form the initial step, they are indicated for diagnostic and therapeutic reasons. For the majority of brain tumors gross total resection provides the best survival rates for all age groups, but may be followed by severe post-treatment morbidity. Postoperative deficits often persist and compensation is less probable in the adolescent than in the pediatric patient. Radiotherapy is applied initially for unresectable tumors as brainstem glioma, for residual tumors postoperatively, and to prevent leptomeningeal spread. Treatment related morbidity such as neuropsychological deficits, endocrine dysfunctions, skeletal malformations and the risk for second malignant neoplasms represent severe sequelae. Tumor resection is the initial treatment option for craniopharyngioma and has an important impact on survival rates. Controversy exists on the extent of the surgical intervention because of severe postoperative damage after extensive resection. Sub-total resection, followed by focal radiotherapy can offer comparable survival rates and reduces endocrine and even neuropsychological sequelae.

In germinoma radiotherapy of the total craniospinal axis is recommended as the only treatment procedure in patients with leptomeningeal spread. Survival rates from 90% to 100% are reported. Alternative strategies to reduce radiation doses consist of intensive chemotherapy and focal field irradiation; they show comparable survival rates but increased tumor relapses. The role of Chemotherapy is under discussion. Adjuvant chemotherapy has been demonstrated to improve tumor control in children with medulloblastoma. Randomized trials show some benefits of adjuvant chemotherapy for anaplastic astrocytoma and ependymoma. Since only 20% of the adolescent cancer patients participate in those trials, compared to 90–95% of children, and compliance is poor, age specific data are insufficient.

3.5.7 Neurosurgical Aspects of Brain Tumor Therapy in Adolescents

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Brain tumors are uncommon in the adolescent population. Surgical treatment of brain tumors in adolescents require neurosurgical principles that are being used in the pediatric as well as in the adult population.

Clinical symptoms, therapeutic options and prognosis are defined by the histological nature of the tumor as well as by its localization and extend in the brain. Primary goal is to cure the patient and enhance or at least preserve his quality of life without causing supplementary neurological, behavioral or cognitive changes. Because of the variable tumor localizations and histological types, determination of further therapeutic steps should be an interdisciplinary decision, since every case invariably demands an individual strategy.

In case of acceptable morbidity, microsurgical tumor removal is the therapy of choice. Retrospective studies have demonstrated the beneficial effect of radical tumor resection concerning long term prognosis. Sometimes this decision making is more difficult due to the localization of the tumor. In those cases a stereotactic biopsy may provide additional information about the dignity of the tumor and therefore be of essential importance for further management which can be microsurgery after all.

In case of diffuse infiltrating tumors involving eloquent brain areas tumor resection is of no benefit to the patient. Stereotactic biopsy will provide the diagnosis which is needed for subsequent therapy which can be radiotherapy or chemotherapy.

3.5.8 The Big Challenge – Developmental Tasks of Adolescents Suffering from Cancer

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The adolescents’ situation is marked by developmental tasks that are part of the normal transition and are determined by biological, social and psychological factors. The diagnosis cancer causes major changes in the adolescents’ daily routine and also threatens coping with these tasks. In order to understand the adolescents’ suffering it is necessary to consider their specific situation of life. Only then one will be able to help them to cope with their illness and improve the quality of their daily life.

Which developmental tasks for adolescents are threatened by the diagnosis cancer? It is difficult to accept ones physique and to use one’s...
body effectively while experiencing physical discomfort like pain, weakness and illness, and temporary bodily changes such as weight gains or losses, loss of hair, or even irreversible changes, such as amputation and sterility. It is also very hard for the adolescent patients to establish emotional and psychological independence from parents, since because of their illness they need a safe, secure and supportive relationship to their parents. Hospitalizations minimize their contact to peers, so that it is very difficult for them to develop stable and productive peer relationships. The task of selecting and preparing for an occupation and developing adult vocational goals is one part of the normal process of establishing a personal identity. In the case of the adolescent patients, these are questioned by the life-threatening nature of the disease.

Consequences: Task of the psychological staff is not only to support the adolescents in coping with illness-related stressors but also enhance them to face the developmental tasks. It is an important part of the rehabilitation process to catch up on developmental setbacks after therapy. The presentation shows the developmental tasks of adolescence and the illness-related stressors which prevent adolescent cancer patients from coping with these tasks. The developmental process will be shown with two case studies.

### 3.6 Clinical Studies

#### 3.6.1 Federal Republic of Germany: A ‘Developing’ Country for Clinical Trials?

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Clinical Studies meanwhile are highly regulated by both national legislation and international guidelines (ICH – GCP: International Conference on Harmonization – Good Clinical Practice Guidelines). These procedures – equally valid for drugs, medicinal products and all other diagnostic and therapeutic measures – are enforced for the protection of the patient as well as for the quality assurance of science. For the global recognition of data obtained in clinical trials the adherence to these guidelines and relevant QA-procedures is mandatory. For the last 25 years Germany has not been among those places primarily chosen by international industrial and public sponsors to perform high class clinical trials for either product development or optimizing therapeutic measures. Overviews over the publications of controlled clinical trials in medical journals recognized internationally place Germany behind all major industrialized countries of the western hemisphere into the middle class of clinical science. This experience, however, has been challenged by both public sponsorship and the scientific medical community of Germany in recent years with the development of so-called Clinical Trial Centers at several university hospitals in Germany.

These measures for an adequate infrastructure combined with an extended concept of teaching clinical trial methodology and conduct of clinical studies within these hospitals have substantially contributed to a more professional view of clinical research and will subsequently improve the quality of clinical trials in our country. The ZKS – Center for Clinical Trials at the University Hospital in Freiburg is one of the model institutions already fully functioning as service center for clinical trials on-site as well as for multicenter clinical projects.

#### 3.6.2 Methodological Requirements in the Conduct of Clinical Trials

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Methodological requirements in the conduct of clinical trials are outlined in numerous scientific papers, text books, and also in regulatory guidelines for drug development and approval issued by the International Conference on Harmonization (ICH). These guidelines, originally intended for trials performed by the pharmaceutical industry for the market approval of drugs, are now also regarded as valuable guidelines for every type of clinical study. Of special concern from a biometric point of view is the guideline E9 ‘Statistical Principles for Clinical Trials’. In this presentation, we want to highlight the most important key concepts and issues, which not only statisticians should be aware of, but also every clinician involved in the conduct of clinical trials. The focus is on basic concepts for bias reduction by adequate study design, conduct, and analysis, being illustrated by examples.

#### 3.6.3 The Multinational Multicentric Clinical Study: An Example

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Vaccination with IGN101 in patients with non-small-cell-lung-cancer (NSCLC) Until now the systemic adjuvant treatment of resectable NSCLC does not improve the oncological results. Most of the patients (up to 70%) die due to distant metastases after radical resection. Specific vaccination was performed in phase I trials using vaccines which imitate antigens on the tumor cell surface. We conduct a prospective, randomized, double-blind, placebo controlled multicenter Phase II/III study in patients with radical resected bronchial carcinoma stage II-IIia. The vaccine induces antibodies to EpCam-Antigen. The objective is to assess the relapse free survival time in patients who underwent R0 resection for stage IIA/B or IIA NSCLC followed by adjuvant vaccination with IGN 101, as compared to placebo. Further on the study should determine the safety, tolerability and immunogenicity of multiple subcutaneous injections of IGN 101. After informed consent, first vaccination is applied within 3 weeks after radical resection. The vaccination is repeated after 2, 4 and 10 weeks and continues every 3 months. Follow up consist of physical examination, ultrasound of the abdomen, chest x-ray and laboratory tests including immunological investigations. 420 patients should participate in the study. The study ends 24 months after enrolment of the last patient. All data are registered in an online case report form (eCRF) with autoquery system. The trial will be analyzed according to the intention-to-treat principle. The relapse free survival rates in both treatment arms will be estimated by the Kaplan-Meier method.
3.6.4

Multimodal Treatment within a Clinical Trial –
A Challenge for Both the Scientist and the Clinician

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Surgical resection has been the standard of care for treatment of resectable esophageal cancer. However, the chance of cure using this modality still remains low with around 20%. The tempting hypothesis that cure rates can be improved by the use of combined modality treatment in the neoadjuvant setting using chemoradiotherapy preoperatively, has not been conclusively confirmed in prospective trials so far. The European Organization for the Research and Treatment of Cancer (EORTC) has initiated a trial for patients with newly diagnosed and localized esophageal cancer (stage I/II according to UICC classification). Patients are randomized either to standard treatment (surgery) or to experimental treatment with preoperative chemotherapy (5-FU, 45 Gy) followed by the same surgical procedure as in the standard arm. The study aims at a survival benefit of 15% of the experimental arm as compared to standard treatment. Furthermore disease free survival, quality of life and perioperative morbidity will be evaluated. After extensive discussion within the interdisciplinary network it was decided that the hospital would participate in this trial. Before the first patient can be included into this trial at our hospital, a variety of legal, ethical and logistical preparation has to be performed: i) adjustment of the patient informed consent form according to the local rules, ii) acceptance of the study protocol by the local ethics committee, iii) contract between the university and the sponsor, iv) involvement and preparation of the medical, nursing, technical, study nurse and pharmacy teams for the study, v) finally an initiation visit, with all persons taking responsibility within the study. These steps required for preparation of each clinical study will be presented with respect to the above mentioned EORTC study.

3.6.5

Therapy Optimization and Quality Assurance in
Multi-Center Clinical Trials

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Therapeutic trials in the field of oncology regularly serve two purposes. They expand our current knowledge and meet the obligation to deliver medical care. Therapeutic trials may investigate the effect of new drugs or new indications for known drugs (Arzneimittelstudien). These trials are subject to the regulations of pharmaceutical law (AMG) and may be sponsored by pharmaceutical industry. Trials in oncology may also serve the purpose of improving current standard care (Therapieoptimierungssprüfung, TOP). With consecutive TOPs survival of children with cancer and adults with leukemia and lymphoma could be improved considerably. A TOP will evaluate a rationally developed therapeutic concept for patient benefit. A generally accepted often multi-modal treatment strategy is to be optimized and the standard of patient care to be improved. Aims of TOPs are to minimize side effects or late sequelae of therapy, study aspects of quality of life or investigate cost-benefit relationships. TOPs are conducted within regular medical care. In oncology, TOPs guarantee that the cancer patient receives adequate and state of the art care. Inclusion criteria for a TOP should be broad as to enroll all patients with a specific form of cancer. TOPs are prospective generally multi-center clinical trials. Therapy within a TOP is delivered according to protocol. For each defined clinical situation (kind and stage of tumor, age of patient, presence of other illnesses) the protocol describes the form of therapy to be delivered. Protocol violations and any variation from standard therapy may impose a risk for the patient while resulting in a lower cure rate. For each registered patient, therapy, side effects of treatment and outcome are documented and centrally evaluated. There is continuing surveillance of therapy and side effects by the study chair person. TOPs may require (or offer) reference evaluation of locally performed services like evaluation of pathology, molecular genetics, immunophenotyping, imaging studies or radiation therapy planning. Local physicians can discuss individual patient problems with the TOP chair person or the panel of reference experts. The patient enrolled in a TOP is given detailed information on therapy and its implications and gives consent for study participation and data handling. Although it is generally recognized that a TOP is a powerful instrument of quality control important issues remain unsolved. One of the most burning questions concerns the financing of TOPs. Research organizations do not want to finance TOPs because TOPs deliver standard care; health insurances do not feel obliged to pay for TOPs in addition to their regular reimbursements; and hospitals point out that costs for TOPs were never part of their frozen budgets. Another area of concern is off-label use of drugs in TOPs. Specifically in pediatric oncology most TOPs include drugs which have a long tradition in childhood cancer, but have never been registered by pharmaceutical industry for this specific indication. Separation of TOPS from pharmaceutical studies is also blurred once a study question concerns the efficacy of additionally introduced chemotherapeutic agents. Not surprisingly, questions whether patients in TOPs have to be insured and what subject is to be insured remain controversial. In summary, TOPs are one of the most powerful instruments to improve survival of cancer patients. It is of utmost importance that TOPs receive more attention by public opinion, politicians and insurance companies.