Combined Radiochemotherapy – State of the Art?

‘The smaller the radiation volume, the higher the total dose and the lower the acute toxicity as well as the late effects on neighboring organs.’

This basic tenet of radiotherapy prompted the development of sophisticated radiotherapeutic equipment and techniques. Their purpose is to provide high-dose, low-volume irradiation and intensity-modulated radiotherapy. These are the only modalities ensuring accelerated radiotherapy. Ever since chemotherapy was introduced decades ago, efforts have been made to improve local tumor control and survival at a better quality of life by combination regimens. The role of chemotherapy, both systemically and locally, in anticancer treatment is uncontested. The possibility that the drugs may have additive effects (regardless of their mechanisms of action) when given concurrently with radiotherapy has been the subject of numerous clinical trials in the past few decades. The objectives of combined radio- and chemotherapy are twofold: local cytotoxicity and local radiosensitization of the tumor on the one hand and control of microscopic metastatic disease on the other. Chemotherapeutic drugs may be given either neo-adjuvantly, simultaneously or in between. This is not the case when radiosensitization is desired. In this case chemotherapy must be administered simultaneously to potentiate the sublethal damage induced by radiotherapy and prevent the repair of potentially lethal radiation-induced damage. The interaction of chemo- and radiotherapy may be subadditive, additive or supraadditive. Depending on the intent of treatment, sensitizing radiochemotherapy may be definitive, neo-adjuvant or postoperatively adjuvant.

Definitive primary radiochemotherapy is mainly designed to salvage organs and function and to preserve the esthetic appearance. Numerous trials showed combined radiation and chemotherapy to be an effective definitive treatment for all stages of carcinoma of the anal canal. The most widely used regimens contain cisplatin, 5-fluorouracil (5-FU) and mitomycin C. Combined treatment regimens were shown to spare 80% of patients a colostomy over a 5-year period. Salvage abdominoperineal resection for incomplete tumor control or recurrent cancer is only needed in a small percentage of cases. Head-and-neck cancers are also increasingly treated by combined primary radiotherapy with promising success, so that

salvage operations with intent to cure can be reserved for poor responders or patients with recurrent tumor growth. For patients with small- or non-small-cell lung cancer, advanced non-resectable pancreatic cancer and locally advanced esophageal cancer, primary radiochemotherapy has become indispensable, as documented by numerous trials. Two recent reports on primary definitive combined radiochemotherapy of cervical cancer in the New England Journal of Medicine showed that patients receiving cisplatin or cisplatin + 5-FU fared significantly better in terms of local tumor control and survival. In one of the reports local tumor control and survival were significantly better despite pelvic irradiation alone versus irradiation of the pelvis and the para-aortic nodes. The role of definitive radiochemotherapy in the management of Hodgkin’s and non-Hodgkin’s lymphoma is uncontested. In these indications irradiation is increasingly performed as low-volume involved radiotherapy.

The primary benefits of neo-adjuvant combined radiochemotherapy are downstaging and downsizing of the tumors so that patients are eligible for R0 resections to salvage organs and to maintain their function. But neo-adjuvant combined radiochemotherapy also devitalizes tumor cells so that peri-operative tumor cell seeding is minimized. In a comparative trial of rectal cancer patients, neo-adjuvant radiochemotherapy was shown to provide better local tumor control and higher survival rates than postoperative radiochemotherapy. As the vasculature is preoperatively still intact, the tumor tissue is well oxygenated so radiosensitization is facilitated and homogeneously high concentrations of the chemotherapeutic agents can be expected. In rectal cancer patients, 5-FU and leucovorin are the drugs most widely used for neo-adjuvant radiochemotherapy. In more recent trials, 5-FU and leucovorin were combined with oxaliplatin or irinotecan. In the most recent reports, neo-adjuvant radiochemotherapy is being advocated for bulky stage-1B cervical cancer with a significantly better outcome in terms of progression-free survival and overall survival than on neo-adjuvant radiotherapy alone. Neo-adjuvant radiochemotherapy with cisplatin and 5-FU also has a place in head-and-neck cancers. In soft tissue sarcoma combined neo-adjuvant radiochemotherapy is being used both as primary treatment modality and for recurrent tumor growth.

Adjuvant combined radiochemotherapy is administered both simultaneously and sequentially for all tumor entities, its main purpose being the control of locoregional and distant micro-metastases. Depending on the type of tumor, specific chemotherapeutic regimens are used for adjuvant treatment.

Combining chemotherapy with radiotherapy for neo-adjuvant, primary definitive and adjuvant treatment, provides the basis for conformation and intensity-modulated radiotherapy, both of which help to minimize radiation-induced side effects.

For the radiotherapist chemotherapy has become an indispensable and very helpful tool, which may well find more and

more indications in the future. Its local cytotoxic, radiosensitizing and tumor-debulking effects improve local tumor control, while its systemic action reduces metastatic tumor spread.

Whether or not novel chemotherapeutic agents will improve the drug-radiation interaction in terms of a supra-additive effect will have to be determined in further trials. The optimal fractionation doses and the maximum cumulatively tolerated doses of radiotherapy combined with chemotherapy for minimizing additive side effects will also have to be the subject of future studies.

A. Schratter-Sehn, Wien