Role of Adjuvant Chemoradiotherapy for Abdominal Malignancies

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Key Words

Adjuvant therapy · Chemoradiotherapy · Gastric cancer · Pancreatic cancer · Rectal cancer

Abstract

The rationale for combining surgery, radiotherapy and chemotherapy is discussed and the clinical results seen with surgery and adjuvant radiochemotherapy in three major abdominal malignancies are reviewed. A systematic approach to the literature was used. In rectal cancer, postoperative radiochemotherapy is an established treatment, although there is weak scientific support for the combined approach. The same clinical gains can also be reached much more easily with preoperative radiotherapy. In gastric cancer, a recent large randomised trial showed improved survival from postoperative radiotherapy. This was not seen in a comparably large trial in pancreatic cancer. The reasons for the different results according to primary tumour site are discussed. It is argued that adequate coverage of all adjacent regional lymph node stations is necessary for an effect on survival.

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Introduction

Abdominal adenocarcinomas are frequently seen, and in the Western world, they constitute about every fourth malignancy. Since prognosis is generally poorer than for other malignancies, approximately every third cancer death is attributed to an abdominal malignancy. The prognosis is particularly poor in those malignancies starting in the pancreas, liver and biliary systems, slightly better in the stomach and more favourable in the colon and rectum. Although improvements in survival have been seen during past decades, they are generally modest at best, and not immediately ascribed to better treatments [1–3].

Surgery is the predominant and most important therapy; however, frequently it is not possible due to an inextirpable primary or the presence of distant spread. Also, in patients where apparently radical surgery has been performed, a substantial number will have recurrence due to microscopic deposits locoregionally or at distant sites. The aim of adjuvant therapy is to kill those deposits to reduce the number of recurrences and thus improve cancer-specific and overall survival.

The outcome after surgery has improved, although this is mainly due to a more favourable postoperative out-

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come and a concentration of fewer surgeons, and not so much to better oncologic results. In rectal cancer, it is indisputable that better lateral clearance, generally meaning a total mesorectal excision, together with the recognition that not every general surgeon should operate on rectal cancer, has improved the oncologic results in terms of both fewer local failures and improved survival [4–6]. This has not, however, been tested in randomised trials. In gastric cancer, it is generally recognized that a D1 resection is better than less than D1 (D0), whereas it is still an open question whether a more extensive D2 resection will further improve the results [7, 8].

Rationale for Adjuvant Chemotherapy

Abdominal adenocarcinomas generally show low or very low sensitivity to chemotherapy. Thus, in metastatic disease, cure is impossible, a complete remission is rarely seen (0–5% of patients) and a partial remission is seen in between 5 and 50% of patients, depending upon the primary tumour site. A complete remission, i.e. disappearance of all visible disease, means that at least 1 or 2 logs of cells (out of at least 9 or 10 logs of cells present prior to therapy) have been killed, whereas a partial remission generally means that the number of tumour cells has been reduced by less than 1 log of cells. The remissions, even if complete, are generally short-lived, i.e. median 4–8 months, indicating that most tumour cells are resistant to therapy [9].

Subclinical tumour deposits, responsible for recurrences after a primarily radical surgery, may contain up to about 8 logs of cells, or be about 5 mm in diameter. It is likely that the tumour cells in a subclinical deposit are more sensitive to cytostatic drugs than those in a visible deposit due to generally better vascularization and a higher number of proliferating cells. Thus, it is possible that not only one or, at the most, two logs of cells are killed by chemotherapy but rather a few logs of cells. Adjuvant chemotherapy in Dukes' C colon cancer prevents approximately every fourth to third recurrence, i.e. it kills on average 2–3 logs of the up to 8 logs of cells that may be present per deposit after surgery [10]. The situation is analogous to that in moderately sensitive breast cancer, where about every third recurrence is prevented by approximately 6 months of adjuvant chemotherapy [11, 12]. These average cell-killing effects are, of course, a statistical phenomenon; in some patients with sensitive tumours, more cells can be killed, whereas in others, no tumour cells are killed. However, if the number of cells is

high, as in established metastatic disease, chemotherapy will not kill all the cells even if the tumours turn out to be very chemosensitive.

Dose-Response Relationships to Radiotherapy

Abdominal adenocarcinomas are, like most other epitheloid malignancies, more sensitive to radiotherapy than chemotherapy. Radiotherapy to a dose that is tolerable to a reasonably large volume of the abdominal cavity has the capability to kill up to about 10^8 – 10^9 cells per deposit. The response to radiotherapy of macroscopic disease is generally considered to be steep, whereas the response to radiation of subclinical disease, which may contain from 10^0 up to 10^8 cells, is linear, i.e. even a low dose has the capability to kill all the cells that may be present in some patients, whereas a higher dose has the capability to eradicate all subclinical cancer deposits in a higher proportion of the patients [13, 14]. A dose of about 50 Gy over 5 weeks (or a comparable dose using other fractionation schedules [15]) has the capability to prevent a recurrence within the irradiated volume in about 85–90% of patients. This knowledge is mainly based upon studies in breast and head and neck cancer. It is, however, likely that subclinical disease of most solid tumours respond to about the same extent [14]. The experience in rectal cancer shows that it responds similarly [16, 17]. Thus, even if no direct knowledge is available for gastric and pancreatic cancer, it is not likely that these tumours will respond fundamentally differently. Consequently, even if, for example, pancreatic cancers as a group frequently contain genetic changes that may be associated with poor radiation sensitivity [18–20], there is reason to believe that the results seen in other gastrointestinal cancers potentially can also be seen in pancreatic cancer.

Much evidence indicates that preoperative radiotherapy is more dose-effective than postoperative radiotherapy, i.e. a certain dose has a higher probability of eradicating all subclinical cells in a surgically non-disturbed tissue than after the surgery [13, 17]. Repopulation of cells in the postoperative phase and a greater probability of hypoxia in the surgical bed are the two most likely reasons for the lower efficacy of postoperative radiotherapy. It is possible that a dose of about 60 Gy is required postoperatively in order to reach the same reduction as can be achieved using 50 Gy preoperatively.

Surgery, Chemotherapy, Radiotherapy or All Three?

Surgery will remain the most important method to remove the many tumour cells that are present in a visible tumour like a primary abdominal adenocarcinoma within the foreseeable future. The disadvantage with surgery is the morbidity that is seen once it aims at removing microscopic deposits from large tissue volumes. Radiotherapy has the advantage of covering a larger tissue volume with less morbidity than surgery, and eradicating all the tumour cells provided they are microscopic in size. The disadvantage with radiotherapy is that large volumes of the abdominal cavity cannot be irradiated to sufficiently high doses. The relations between tolerable radiation doses and volumes within different parts of the cavity are complex and only partly known. The entire cavity would hardly tolerate doses higher than 15–18 Gy, whereas limited volumes (a few decilitres) could tolerate 60 Gy or more. The tissue volumes at risk of containing tumour deposits in connection with a primary abdominal cancer can amount to several litres. Such volumes can hardly tolerate doses higher than 40–50 Gy. Larger volumes can generally be irradiated in the pelvis than in the abdomen.

With these figures in mind, and with the knowledge that the dose-response relationship of subclinical disease to radiotherapy is linear [14], radiotherapy has a reasonable chance of reducing local failure rates. Preoperative radiotherapy has an even higher probability than postoperative radiotherapy.

Cytostatic drugs or, in the future, more sophisticated drugs have the definite advantage of no geographical restriction. The efficacy, however, is still limited. It can be estimated that the cell-killing effect of 6 months of adjuvant chemotherapy for breast and colon cancer, for example, corresponds to a (whole-body) dose of about 15 Gy (prevents every fourth to third recurrence).

Radiotherapy and chemotherapy may co-operate spatially but may also, provided the cell-killing effects are independent of each other, be additive. Synergy is theoretically possible and has been much aimed at, but has not yet been seen clinically [21–24]. Yet, clinical gains have been seen in various tumour types, predominantly squamous cell carcinomas in the head and neck, oesophagus, lung, cervix and anus, but also in abdominal adenocarcinoma, using concomitant radiochemotherapy [25–28]. Radiochemotherapy has also gained much popularity, and whenever radiotherapy is used for a gastrointestinal malignancy, it is preferentially given with concomitant chemotherapy [29]. The scientific support for this use in

abdominal malignancies is not, however, particularly strong, as will be discussed below. Since spatial co-operation is highly relevant, and additivity may be seen against loco-regional disease, it appears as if the best radiochemotherapy combination is when both modalities can safely be given together at the same doses as when used alone, i.e. the toxicity is non-overlapping. Thus, if only a fraction of the chemotherapy dose, for example, can be given with radiotherapy because of acute toxicity, this would, according to the opinion of this reviewer, disqualify the combination from further testing. Rather, the opposite has happened. The finding that only low doses of gemcitabine could be given with radiotherapy (or only low doses of radiotherapy with normal doses of gemcitabine) has, on the contrary, been taken as an indication of a promising combination to explore further [23, 30]. The spatial co-operation will be absent and although selective synergy for tumour cells is still possible, this is not a likely event.

Clinical Effects in Abdominal Malignancies

Adjuvant chemoradiotherapy to decrease the risk of recurrence, and thus improve survival, has mainly been tried in rectal cancer, but also in pancreatic and gastric cancer. The use in other abdominal cancers is limited [31, 32] and will not be further reviewed here.

Rectal Cancer

In patients with a technically resectable cancer, generally constituting 85–90% of patients with a newly diagnosed rectal cancer, radio(chemo)therapy has been extensively used to lower unacceptably high local failure rates seen after surgery alone [33, 34]. The radiotherapy has been given either before or after the surgery, or occasionally both before and after. Large randomised trials have shown that preoperative radiotherapy can substantially decrease local failure rates and, unless counterbalanced by increased postoperative mortality, as seen in some trials [35], slightly improve overall survival [36, 37]. In this situation, radiotherapy has seldom been combined with chemotherapy, although this is being tested in an ongoing trial by the European Organization for Research and Treatment of Cancer (EORTC; protocol 22921).

Randomised trials have also shown that postoperative radiotherapy may decrease local failure rates, although to a lower extent than reached by preoperative radiotherapy [17], but without any influence on overall survival. Postoperatively, radiochemotherapy, rather than radiotherapy alone, has been used in several of the trials and has

Table 1. Postoperative radiotherapy, chemotherapy or radiochemotherapy: results of randomised trials in rectal cancer stages II + III (trials only comparing two radiochemotherapy regimens are not included in the table)

Trial, year	Study arms	Patient population	Results	Comments
GITSG 7175 1985, 1986 [38, 39]	A: surgery alone B: surgery + RT 40–48 Gy C: surgery + CHT (MF) D: surgery + RT + 5-FU + CHT (MF)	1975–1980 202/227 eligible A: 58 pts B: 50 pts C: 48 pts D: 46 pts	5-year local failure rate A: 24%, B: 20%, C: 27%, D: 11% (NS) 6-year overall survival A: 28%, B: 43%, C: 43%, D: 57% (p = 0.05)	small trial, prematurely interrupted, supports the benefit of postop RTCHT; increased acute toxicity was seen
NCCTG 794751 1991 [40, 74]	A: RT 45 Gy ± boost 5.4 Gy B: same RT + 5-FU + CHT (MF)	1980–1986 204/209 eligible A: 100 pts B: 104 pts	5-year local failure rate A: 25%, B: 14% (p = 0.04) 5-year overall survival A: 47%, B: 58% (p = 0.04)	supports the benefit of combined RTCHT over RT alone; increased acute toxicity, particularly diarrhoea (grade 3–4 22 vs. 4%, p = 0.001)
NSABP-R01 1988 [41]	A: surgery alone B: surgery + RT 46.5 Gy C: surgery + CHT (MOF)	1977–1986 555/574 eligible A: 185 pts B: 184 pts C: 187 pts	5-year local failure rate A: 25%, B: 16%, C: 21% (NS) 5-year overall survival A: 43%, B: 41%, C: 53% (p = 0.05)	no benefit was seen with postoperative RT; a survival benefit was seen with CHT alone, challenging the results of the GITSG 7175 trial – the benefit was restricted to males
ECOG-EST 1991 [46]	A: RT B: CHT (MF) C: RT + CHT	1986–? 248 eligible 237 evaluable	overall survival A: 46%, B: 47%, C: 50% (NS)	only reported as an abstract; no concomitant CHT was given; gives no evidence of any survival benefit
Tveit et al. 1997 [42]	A: surgery alone B: surgery + RT + 5-FU	1987–1991 A: 72 pts B: 72 pts	local failure rate A: 32%, B: 11% (p = 0.01) overall survival A: 49%, B: 63% (p = 0.05)	small trial, but supports the benefit of concomitant RTCHT without prolonged CHT
Cafiero et al. 2000 [75]	A: RT 50 Gy B: CHT × 1 + RT + CHT × 5 (5-FU + levamisole)	1992–1998 A: 108 pts B: 110 pts	local failure rate A: 15%, B: 21% (NS) projected 5-year survival A: 56%, B: 39% (NS)	no benefit was seen with CHT in addition to postoperative RT; increased acute toxicity, with significantly more severe enteritis (p = 0.03)
NSABP-R02 2000 [44]	A: CHT (MOF or FLv) B: CHT + RT 45 Gy + boost 5.4 Gy + 5-FU + CHT	1987–1992 694/742 eligible A: 348 pts B: 346 pts	8-year initial local failure rate A: 14%, B: 8% (p = 0.02) 8-year overall survival A = B: 58% (p = 0.9)	RT with CHT decreased local failure rates but did not improve survival

CHT = Chemotherapy; FLv = 5-FU + leucovorin; MF = methyl-CCNU + 5-FU; MOF = methyl-CCNU + vincristine + 5-FU; pts = patient(s); RT = radiotherapy; RTCHT = radiochemotherapy; NCCTG = North Central Cancer Treatment Group; ECOG = Eastern Co-operative Oncology Group; NS = not significant.

tended to decrease local failure rates and significantly improve survival compared with surgery alone or surgery and postoperative radiotherapy (table 1) [38–42]. A survival benefit was, however, seen with postoperative chemotherapy alone without any radiotherapy in the trial (Protocol R-01) conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) [41].

In 1990, a US NIH Consensus Conference recommended postoperative chemoradiotherapy as standard treatment for rectal cancer in stages II and III [43]. The consensus statement was based upon the results of three of the randomised trials mentioned above [38–41]. The results of the studies can, however, be interpreted differently; it is actually possible that the survival benefit may be ascribed to the systemic effects of the chemotherapy

component and not to improved local control offered by, for example, radiosensitization. The Gastrointestinal Tumor Study Group (GITSG) trial was severely underpowered to reveal any benefit from either radiotherapy or chemotherapy alone [38, 39]. This conclusion is further supported by a follow-up trial by the NSABP (Protocol R-02). In that trial, postoperative chemotherapy was given to all patients, whereas postoperative radiotherapy was randomly assigned to half of the 694 eligible patients. The radiotherapy had no beneficial effect on disease-free or overall survival, although it slightly reduced the cumulative incidence of locoregional relapse from 13 to 8% at 5-year follow-up (p = 0.02) [44]. The role of the radiotherapy component in the postoperative radiochemotherapy with respect to the survival gain can thus be questioned. If

Table 2. Postoperative chemotherapy or radiochemotherapy: randomised trials in pancreatic cancer (trials only comparing two active treatments are not included)

Trial, year	Study arms	Patient population	Results	Comments
Bakkevold et al. 1993 [49]	A: surgery alone B: surgery + CHT (FAM)	1984–1987 61/110 randomised A: 31 pts B: 30 pts	median survival A: 11 mts, B: 23 mts ($p = 0.02$) 2-year overall survival no difference	small trial; a short-term benefit was seen; toxicity was significant, which could diminish the effect since only 13 patients (43%) completed 6 cycles
Amano et al. 1999 [50]	A: surgery alone B: surgery + CHT (MF)	1988–1992 158 pts	5-year survival A: 18%, B: 12% (NS)	only reported as an abstract; no benefit was seen; also included patients with periampullary and biliary cancer
GITSG 1985 [51]	A: surgery alone B: surgery + RTCHT (40 Gy + 5-FU)	1974–1982 43/49 eligible A: 21 pts B: 22 pts	2-year survival A: 18%, B: 43% 5-year survival A: 8%, B: 18% ($p = 0.04$)	very small trial that took many years for several hospitals to complete; shows a survival benefit with RTCHT; discussed extensively, but considered by some sufficient evidence for postoperative RTCHT
EORTC 1999 [52]	A: surgery alone B: surgery + RTCHT (40 Gy with 5-FU)	1987–1995 208/218 eligible A: 108 pts B: 110 pts	median survival A: 19 mts, B: 25 mts ($p = 0.2$) 2-year survival A: 41%, B: 51% ($p = 0.1$)	trend towards improved survival with RTCHT was seen, but underpowered; 21% of the patients did not receive any therapy; included also periampullary cancers
ESPAC-1 2001 [53]	A: surgery alone B: surgery + CHT (FLv) C: surgery + RTCHT (40 Gy with 5-FU) D: surgery + RTCHT + CHT	1994–2000 no RTCHT: 178 pts RTCHT: 175 pts no CHT: 235 pts CHT: 238 pts	median survival no RTCHT + RTCHT: 16 mts (NS) no CHT: 14 mts CHT: 20 mts ($p = 0.005$)	pts could be randomised to 2 arms or 4 arms in a 2×2 factorial design; no benefit of RTCHT was seen, whereas it was with CHT; the benefit was seen in all strata

CHT = Chemotherapy; FAM = 5-FU + doxorubicin + mitomycin-C; MF = methyl-CCNU + 5-FU; RTCHT = radiochemotherapy; FLv = 5-FU + leucovorin; pts = patients; mts = months; NS = not significant.

radiochemotherapy is used postoperatively, protracted infusion of 5-fluorouracil (5-FU) is superior to bolus 5-FU during the radiotherapy [45]. This treatment may thus be considered as a reference regimen if a combined approach is used postoperatively, since superiority has been shown in one large randomised trial.

Several other randomised trials add information on the relevance of postoperative radio(chemo)therapy. In a Norwegian trial, 144 patients were randomised to surgery alone, and postoperative radiotherapy with bolus 5-FU was given only during the radiotherapy [42]. A clear benefit with respect to both local control rate and survival was seen, indirectly supporting the efficacy of concomitant administration. In another US trial (Eastern Co-operative Oncology Group, study EST 4276), only reported as an abstract in 1991 [46], no influence on either local control rate or survival was seen from sequential postoperative radiotherapy and chemotherapy compared with surgery alone. This apparently negative trial, never published in full, was not considered in the NIH document. Since concomitant chemoradiotherapy was not used, the trial data also indirectly support the relevance of concomitant administration. An Hellenic group studied the value of add-

ing three cycles of bolus 5-FU and leucovorin after one cycle of the same regimen and radiotherapy with bolus 5-FU [47]. No difference could be seen in the trial involving 220 patients, excluding a major influence on survival of the postoperative chemotherapy component. Neither addition of leucovorin nor levamisole to 5-FU and radiotherapy showed an influence on control rates or survival in a large randomised trial including 1,696 patients [48]. Thus, there is no evidence that modulated 5-FU is superior to 5-FU alone when combined with radiotherapy, as is the case when chemotherapy is used alone for metastatic disease [10].

Taking these results together, it is not possible to define an optimal combination of chemotherapy and radiation postoperatively in rectal cancer patients in stages II and III. It is actually not even possible to state that a combination is superior to either modality alone, although this is likely the case.

Pancreatic Cancer

Five randomised studies of adjuvant (radio)chemotherapy following pancreatic resection for cancer are available (table 2). A modified regimen of 5-FU, doxoru-

bicin and mitomycin-C was given every 3 weeks for six cycles after resection in one trial [49]. Of 110 patients with radical pancreatic resection, 61 were eligible for randomisation. The median survival was significantly longer in the treatment group than in the control group ($p = 0.02$). The difference was attributed to a survival benefit in the treatment group during the first 2 years.

A large Japanese randomised study of 158 patients with pancreatic cancer could not detect any benefit of postoperative chemotherapy using 5-FU and mitomycin C [50]. The study showed, however, a significant survival benefit for gallbladder cancer ($n = 112$), but no such benefit was observed for bile duct ($n = 118$) and periampullary cancer ($n = 48$).

5-FU has been used together with external radiotherapy in three randomised trials with a surgery-alone group [51–53]. In the first trial, performed by the GITSG, 5-FU was administered together with 40 Gy of external radiotherapy to 22 patients after radical pancreatectomy [51]. A statistically significant difference in survival was found between the treated patients and the non-treated controls (table 2). Similar results were reported from a phase II study using the same regimen of postoperative radiation and 5-FU treatment [54]. In these studies, good tolerance to the treatment regimen was noted.

In the second trial, performed by the EORTC [52], split-course chemoradiation as used in the GITSG trial was administered without maintenance chemotherapy. A total of 218 patients were randomised, 119 with pancreatic head cancers and 109 with periampullary cancers. In patients with pancreatic cancer, median and 2-year survival rates tended to be better for patients randomised to chemoradiotherapy than for patients randomised to the control condition. There were no significant differences among patients with periampullary cancers. Overall, therapy was well tolerated, but 22% of the patients in the treatment group did not receive any treatment because of postoperative morbidity or patient refusal after randomisation.

The European Study Group for Pancreatic Cancer (ESPAC-1) assessed the role of postoperative chemoradiotherapy or chemotherapy in a randomised trial of 541 patients with ductal pancreatic adenocarcinoma [53]. A two-by-two factorial design was used. After resection, patients were randomly assigned to adjuvant chemoradiotherapy using a split course with 40 Gy and 5-FU or chemotherapy with 5-FU-leucovorin according to the Mayo schedule for 6 months. Patients could be randomised to observation, chemoradiotherapy alone, chemotherapy alone or both. After a median follow-up of 10 months for

patients still alive, the results showed no benefit of adjuvant chemoradiotherapy, whereas there was evidence of a survival benefit with adjuvant chemotherapy (table 2). Toxicity data were available only in a subset of patients, and 27% reported serious toxic effects, predominantly when chemotherapy was used alone. The follow-up is not long enough to assess whether the proportions of patients alive after 3 or 5 years will differ.

Evidence that adjuvant treatment should routinely be used in pancreatic cancer is presently not available. The small US GITSG study [51] has been discussed extensively during the past 15 years and the interpretation of the apparently positive trial data has varied considerably. The methodological weaknesses of the trial are so pronounced that it cannot form the basis for a recommendation of general treatment outside clinical trials. This is further supported by the EORTC trial [52]. The trial was negative ($p = 0.1$) but underpowered ($n = 119$). A joint committee of US co-operative groups recently reached a conclusion to the contrary [30]. Even if the committee recognized that 'purists will demand to know where the no-treatment arm is to be found', it suggested a study (RTOG 9704) that has two active post-surgical chemoradiation arms [30]. The trial data, together with the positive results of the Norwegian trial [49] and ESPAC-1 [53], indicate, however, that further trials, properly controlled, are important. The ESPAC-1 has rolled into ESPAC-3, randomising between surgery alone, 5-FU with leucovorin and gemcitabine. The future of adjuvant treatment of pancreatic and periampullary cancers is dependent on the results of this and comparable trials.

Two randomised trials have provided some evidence that chemoradiation is slightly superior to either modality alone in patients with inoperable pancreatic cancer. In a trial by the GITSG that included 194 patients, a slight gain in survival was seen when 5-FU was added to postoperative radiotherapy (40 or 60 Gy) compared with radiotherapy alone (60 Gy; median survival 8 vs. 5 months, $p < 0.01$) [55]. Chemotherapy alone (the SMF regimen, streptozotocin, mitomycin-C, 5-FU) was inferior to the combination of 5-FU and radiation (54 Gy; median survival 8 vs. 10.5 months, $p < 0.02$) in a trial involving 43 patients [56]. In yet another randomised trial by the GITSG, doxorubicin and radiation were compared with 5-FU and radiation in 157 patients. In this study, however, there was no evidence of superiority of either schedule [57].

Table 3. Postoperative radio(chemo)therapy: results of randomised trials in gastric cancer

Trial, year	Study arms	Patient population	Results	Comments
Mayo 1974 [59]	A: surgery + RT B: surgery + RT with 5-FU	study period unknown A: 23 pts B: 25 pts	mean survival A: 6 mts, B: 13 mts ($p < 0.05$) 5-year survival A: 0%, B: 12%	included unresected or residual cancers; small trial that showed benefit for RTCHT versus RT alone
GITSG 1982 [60, 61]	A: surgery + CHT (MF) B: surgery + RT (50 Gy) with 5-FU + CHT	1975–1977 90/96 eligible A: 45 pts B: 45 pts	5-year survival A: 7%, B: 16% ($p < 0.05$)	included pts with residual tumour; RTCHT appeared more effective than CHT alone after long follow-up, but showed substantial toxicity with initially inferior survival
EORTC 1989 [62]	A: surgery + RT (55 Gy) B: surgery + RT with short 5-FU C: surgery + RT with long 5-FU D: surgery + RT with short + long 5-FU	1972–1978 A: 30 pts B: 30 pts C: 26 pts D: 29 pts	median survival A: 12 mts, B: 19 mts, C: 15 mts; D: 18 mts ($p = 0.04$)	both curatively and palliatively resected pts included; subgroup analyses show that pro- longed RTCHT may indicate increased chance of long-term survival
US Intergroup 2001 [63]	A: surgery alone B: surgery + RT (45 Gy) with 5-FU + CHT (FLv)	1991–1998 556/603 eligible A: 275 pts B: 281 pts	median survival A: 27 mts, B: 36 mts ($p = 0.005$) 3-year survival A: 41%, B: 50%	large trial which included only radically resected cancers; showed a survival benefit for postoperative RTCHT, seen irrespective of the extent of surgery (D0–2); toxic, but manageable

RT = Radiotherapy; CHT = chemotherapy; MF = methyl-CCNU + 5-FU; FLv = 5-FU + leucovorin; pts = patients; mts = months;
RTCHT = radiochemotherapy.

Gastric Cancer

A great number of randomised trials have explored the value of adjuvant chemotherapy after gastric cancer surgery. Collectively, they do not indicate any relevant survival gain [58]

Four trials, three early and small, and one recent and large, have explored the value of radiochemotherapy in gastric cancer in a controlled way (table 3). In an early randomised trial from the Mayo Clinic, patients with unresected or residual gastric cancers were treated with radiotherapy alone or radiation plus concomitant bolus 5-FU. Mean and 5-year survival were more favourable with combined therapy [59]. The GITSG [60] randomised 90 eligible patients to receive either combination chemotherapy alone (5-FU and methyl-CCNU) or a split course of 50 Gy with bolus 5-FU on days 1–3 of each 25-Gy course of radiotherapy to the regional residual disease, followed by 5-FU plus methyl-CCNU. All patients had histologically proven adenocarcinoma, gross or microscopic local residual tumour and no metastatic disease. Survival was initially inferior for the radiochemotherapy arm because of myelosuppression and nutritional complications. However, with a minimum of 5 years of follow-up, survival was statistically improved ($p < 0.05$) in the combined radiochemotherapy arm [61]. Bleiberg et al. [62] tested the value of various sequences of 5-FU with radiation (55.5 Gy) versus radiation alone after curative

or palliative gastric resection. All long-term survivors with postoperative residual disease received concomitant radiochemotherapy, and 5-FU-based chemotherapy was also associated with improved overall survival ($p = 0.04$). However, when the comparisons were adjusted for the most significant prognostic factors, the difference in survival disappeared. Moreover, no difference was found between treatments in terms of time to progression. The three trials give some support to the superiority of radiochemotherapy compared with radiotherapy, but since they exclusively or predominantly included non-resected or palliatively resected cases, they do not give any information about the role of adjuvant radiochemotherapy.

In the fourth and by far the largest trial, a US Intergroup Study recently reported improved survival after postoperative radiochemotherapy [63]. Altogether, 556 patients with resected gastric cancer were randomly assigned to surgery alone or surgery plus postoperative radiochemotherapy. The adjuvant treatment consisted of one course of 5-FU plus leucovorin over 5 days (Mayo Clinic schedule), followed by 45 Gy of radiation for 5 weeks with 5-FU and leucovorin, followed by two more cycles of 5-FU-leucovorin. An extensive quality assurance (QA) and quality control assessment of the radiotherapy was included in the trial. This procedure revealed inappropriate radiotherapy planning in a large proportion of patients. Forty-four percent of the patients had a D0

lymphadenectomy, i.e. a resection in which not all of the N1 nodes were removed, 36% had a D1 dissection and only 10% a D2 dissection. The median overall survival was longer in the chemoradiotherapy group (table 3). The survival curves indicate that the benefit was maintained beyond 5 years. Toxicity to treatment was predominantly haematologic and gastrointestinal, and grade III or greater toxicity was seen in 41% of the patients.

Why Is Postoperative Radiochemotherapy Effective in Rectal and Gastric Cancer but Not in Pancreatic Cancer?

The randomised trials described above had opposite results concerning the influence of postoperative radiochemotherapy on survival for the three major abdominal cancers. Most oncologists would immediately agree that these results could be anticipated in advance. Firstly, gastric and colorectal cancer show higher sensitivity, at least in the short-term, to both radiotherapy and chemotherapy than pancreatic cancer [10, 58, 64]. Pancreatic cancer contains a number of molecular changes, all suspected to confer chemoradioresistance in other tumours [18, 19, 65], and more frequently has distant metastases than both rectal and gastric cancer. Secondly, the radiotherapy dose used in the pancreatic trial (40-Gy split dose) was lower than the dose in the gastric cancer trial (45 Gy) and in the rectal cancer trials (46–50 Gy). It is difficult to argue against these explanations of the contrasting results between tumour sites.

There is, however, an additional explanation. In the gastric cancer trial, the clinical target volume was clearly defined and included the tumour bed, the regional lymph nodes and a margin beyond the resection margins. Extensive QA and quality control assessments of the radiotherapy plans were made both prior to the treatment and afterwards. Much emphasis has been placed on the radiation techniques in rectal cancer trials [66]. In the pragmatic pancreatic cancer trial, details of the radiotherapy were not given in the publication and only local QA procedures were available. Although not known, it is possible that many patients only had radiotherapy of the tumour bed with margins. Admittedly, it is easy to blame failures on improper ‘whatever you can think of’, and radiation oncologists may in this respect be no exception (some would actually argue that we are among the worst). I would argue that adequate coverage of not only the resection bed but of *all* regional lymph nodes is essential for effective radiotherapy, whether given pre- or postoperatively, and that

this is more important than the radiotherapy dose. It is known, as discussed above, that the dose-response relationship to radiotherapy for subclinical disease is linear and, therefore, some effects could be seen also using rather low doses [14, 16]. Regional node involvement is extremely common in pancreatic cancer. Using sensitive markers (immunohistochemistry, PCR-based techniques), tumor cells can be found in 100% of cases, even in nodes only removed during an extended lymph node dissection [67]. If lymph node metastases are seen, distant metastases are extremely common, albeit not present in 100% of cases. Thus, there may be an opportunity for an effect of regional therapy such as radiotherapy. The regional therapy, whether extended surgery or radiotherapy, must then cover *all* regional nodes at risk of containing tumour cells and not just those easily removed/irradiated.

Compensation for Poor Surgery?

Arguments have been submitted that the radiochemotherapy effect in gastric cancer is only a compensation for poor surgery. These arguments have repeatedly been raised also in rectal cancer radiotherapy. The recently reported total mesorectal excision trial, where surgery was at a higher quality level than was the case in all previous rectal cancer radiotherapy trials [37], clearly showed a benefit of radiotherapy in terms of fewer local recurrences also in combination with optimal surgery [68]. Actually, the relative efficacy of radiotherapy was higher with good surgery than with ‘standard’ surgery, as could be anticipated [69, 70]. The hypothesis could then be raised that the positive radiochemotherapy effects seen in gastric cancer in the US trial [63] would be even larger if the patients had had adequate surgery (all at least a D1 resection). It is then possible that the radiotherapy coverage of the regional nodes must be more complete than is the case if surgery only removes that bulk of the tumour cells in order to lower the risk of failure. The success story in rectal cancer may be a result of rather large clinical target volumes, including not only the nodes close to the bowel but also all lateral nodes [66, 69]. In some of the trials, however, unnecessarily large target volumes were selected, resulting in too much toxicity. Inappropriate techniques further increased radiation burden, and thus toxicity, in some trials [69, 70].

Need for Further Trials

The extrapolations of trial data, including the comparisons made between different abdominal tumour sites described above, are all speculations. Speculations can never form the basis for treatment recommendations. Adjuvant therapy is thus not yet routine therapy in either gastric or pancreatic cancer. If based upon sound clinical and tumour biological knowledge, such speculations can, however, form the basis for hypotheses to be tested in proper trials. Thus, a European initiative for a large gastric cancer trial with good QA of all relevant aspects (staging, surgery, additional therapy and pathology) is urgently needed. In the US, a decision has already been made by some experts that postoperative radiochemotherapy is standard therapy [71]. In the report, detailed descriptions of the radiotherapy portals are given for various localisations of the primary tumour in the stomach.

In rectal cancer, major uncertainties regarding the best adjuvant therapy also remain. In Europe, preoperative radiotherapy is predominantly used, and the short Swedish schedule of 5×5 Gy has gained much popularity [70]. In the US, in contrast, postoperative radio(chemo)therapy is predominantly used [72]. When radiotherapy is given alone, all evidence points to the greater efficacy and tolerability of preoperative delivery [17, 37]. The two most widely used approaches, i.e. preoperative 5×5 Gy over 1 week and postoperative radiochemotherapy over 6 months (radiotherapy over 5–6 weeks), have never been directly compared, although a Polish trial has completed patient recruitment [73]. The 5×5 Gy schedule has been tested against surgery alone in four large trials involving over 4,000 (4,061) patients, and was also found to be

effective with total mesorectal excision, whereas the randomised evidence of a comparable efficacy of postoperative radiochemotherapy is limited to two trials involving a total of 346 patients.

Conclusions

The potentials, but also the limitations of various therapy modalities must be known and considered prior to designing combined therapy protocols. The differences in cell-killing/removal effects and the spatial differences between surgery, radiotherapy and chemotherapy illustrate that clinical gains can be achieved. Randomised trials have also shown that surgery followed by adjuvant radiochemotherapy has resulted in such gains in some abdominal malignancies. The gains have so far been limited, although clinically meaningful at least in rectal cancer. Since the gains are limited, better selection of the patients with the greatest need for additional therapy is required. It is also important in the future to be able to select those who will respond to the additional therapy.

When combining various therapies, timing is also relevant. It is likely that preoperative therapy may result in further gains, and this approach must be tested also at sites other than the rectum. The concomitant administration of radiotherapy and chemotherapy, although very popular and preferred by many, should also be the subject of trials to gain further knowledge about the balance between anti-tumour and normal tissue effects. Finally, more emphasis must be placed on the extent of both surgery and radiotherapy in order to remove as many tumour cells as possible with as little morbidity as possible.

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