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COMBINED TREATMENT MODALITIES IN ESOPHAGEAL CANCER

Should chemotherapy be included?

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The poor prognosis of esophageal carcinoma patients after treatment with local modalities (surgery/radiotherapy) is well known. The purpose of this review is to assess the question whether addition of chemotherapy to local treatment of squamous cell carcinoma of the esophagus has had any beneficial effect on treatment results. In the absence of a sufficient number of randomized trials addressing this issue, data mainly from single-arm studies are discussed. Compiled data from studies on preoperative chemotherapy, preoperative chemoradiation and chemoradiation without surgery suggest that addition of chemotherapy to local treatment (surgery/radiotherapy) might increase short-term survival (2 years) compared to local therapy alone. In the case of chemoradiation without surgery this conclusion is strengthened by results from randomized trials. In general lack of long-term follow-up data limits conclusion whether to recommend the inclusion of chemotherapy into treatment of esophageal cancer or not. Treatment results, however, from studies utilizing combination chemotherapy given concomitant with radiotherapy support the contention that well-designed randomized trials with long-term follow-up should be performed. Outside controlled trials, however, surgery or radiotherapy should still be regarded as standard treatment modalities.

Esophageal carcinoma (EC) is an infrequent malignancy in the Western world. In the United States EC is responsible for only 1.5% of all cancers and the age adjusted incidence in 1984 was 3.5 (male 5.6 and female 1.9) per 100 000 (1). This is comparable to the figures for most parts of Europe including Sweden (male 4.0 and female 1.2 per 100 000) (2). In contrast, in some parts of the world the disease is almost epidemic, as for example in South Africa (incidence of 125 per 100 000 males in Soweto), China (mortality of 436 per 100 000 men in Honan province) and Iran (incidence of 174 and 108 per 100 000 women and men respectively in the province of Mazandaran) (1). For many years more than 90% of esophageal tumors have been squamous cell carcinomas (SCC). A significant change in epidemiology has occurred in the last 10–15 years in the US. The incidence of adenocarcinomas of the distal esophagus and esophageal junction are rapidly increasing, whereas the incidence of SCC remains stable (3, 4). The reason for this change is not clear. In Sweden, however, an increase of both histologies has occurred during the past 20 years and no change of the relation between them has been noticed (2).

The purpose of the present review was to assess the question whether addition of chemotherapy (CT) to local treatment of SCC of the esophagus has had any beneficial effect on treatment results. Esophageal tumors are usually diagnosed at a very late stage when palliation rather than cure may be considered aim of treatment. In the case of palliative treatment, quality of life during treatment and survival would be appropriate factors to analyse and compare. One problem is, however, obvious when the literature on EC is examined. In the material presented an almost invariable lack of data regarding quality of life of treated patients is encountered, no matter if the treatment consists of surgery, radiotherapy or any combined modality. Survival, the other factor that could be compared, is

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more often presented, either as median survival or actuarial survival. Very few large randomized trials evaluating addition of CT to local treatment have been carried out and almost all results presented in single-arm studies relate to selected patient groups where it is likely that patients with bad prognostic factors have been excluded. There are, however, no data to support the idea that selection should be more frequent in trials including CT than for instance in materials presented on surgical treatment alone. Albeit, the studies on different combined treatment approaches have some disadvantages, the follow-up period for most patients is short, so that long-term survival is rarely available and in addition most of the studies include very few patients. In the studies different diagnostic procedures are also utilized giving room for differences in staging of the patients before treatment and at response evaluation. With the above mentioned problems in mind we have performed a compilation of data for different combined modality therapies in EC. Studies included in this review are those published in major journals found by computer aided search (Medline, Cancer lit). Some reports have, however, been excluded. The main reason for this is that conclusions are made on patient materials displaying a mixture of tumor-histologies. To avoid iteration of previously reported patient materials we also have excluded some iterative publications.

The use of compiled data may disregard differences between studies included but we think that it may provide a first basis for the comparison of different modalities. At present there are not enough randomized trials on which a more reliable analysis can be made.

Local and loco-regional treatment

For cases with localized disease surgery is central since it may be curative. One of the main problems, however, has been high operation mortality. In a review of 83 783 patients presented in 1980 the resection mortality was reported to be 29% (22% operative mortality) (5). In more recent reports, however, the mortality rates are lower, even in the range 0–7% (6–8), and in a review of surgical series from the eighties, Müller et al. (9) found resection mortality to be 13%. Unfortunately this has had no impact on survival (9). This is likely due to the inability of surgery to eradicate generalized or even regionally spread tumor which is characteristic in most cases of EC. With surgery as only treatment the 5-year survival for operated patients is around 10% (5). It may be appropriate to point out that at least 30–40% of the total EC population is not included in this figure, i.e. those never considered for operation. To reach a more definitive loco-regional control, other treatment modalities have been tried.

EC is known to be sensitive to radiotherapy (RT), used to obtain not only local but also regional control of disease. With radiation doses of 50–65 Gy curative treatment results have been reported. Mortal complications due to RT are uncommon. Radiomyelitis, one of the most feared complications, is also very seldom encountered. In one material with 865 treated patients, only 4 instances of myelitis were reported, all receiving rather high total dosages (2 patients, 70–75 Gy and 2 patients, 65–67 Gy) (10). In a review the 1-, 2- and 5-year survival for 8 489 irradiated patients is considered to be 18%, 8% and 6% respectively (11). For European studies on radiation therapy with curative intention one of the highest 5-year survival rates (9%) has been reported by Newaishy et al. (12) after treatment of 444 patients with a total dose of 50 Gy (2.5 Gy/fraction).

First-line treatment might be radiation therapy more often for the cervical part of the esophagus than other localizations because of the mutilating operation needed. This in turn probably leads to the inclusion of cases with less advanced disease compared to the patient with usual radiotherapy. In two series the 5-year survival for this location treated with radiation alone is about 17% (12, 13).

In the United Kingdom a prospective randomized multicenter trial of RT versus (vs) surgery for operable EC was started in January 1987. Unfortunately the trial was discontinued after 18 months because of lack of recruitment (14). Thus, the question whether possibly operable SCC of the esophagus is to be treated by RT or surgical resection remains unanswered. To our knowledge there is no ongoing study trying to assess this basic question.

The first combined modality approach when treating EC was preoperative radiotherapy. The assumption was that radiation could shrink the tumor and thereby lead to increased resectability. There are 5 prospective randomized trials with 5-year survival data presented (15–19). The resection rates in these 5 randomized series are high (70–95%) but there is no significant difference between irradiated and non-irradiated patients. Operation mortality is not affected by the preoperative radiation and when it comes to long-term survival no benefit has been demonstrated for preoperative RT. In three European materials; Launois et al. (15) (39–45 Gy in 8–12 days) reported 9.5% vs 11.5%, Gignoux et al. (16) (33 Gy in 12 days) 10% vs 9% and Arnott et al. (17) (20 Gy in 10 days) 9% vs 17% 5-year survival for preoperatively irradiated and directly operated patients respectively. The lack of benefit regarding survival for preoperative RT is further substantiated by two Chinese studies (18, 19). However, in a recent publication Nygaard et al. (20) argued that preoperative irradiation has a beneficial effect on intermediate term survival (3 years). In the study, 186 operable patients were randomized to receive surgery alone, preoperative CT (cisplatinum + bleomycin), preoperative RT (35 Gy, 1.75 Gy/fraction) or preoperative CT + RT (cisplatinum + bleomycin followed by 35 Gy). The 3-year survival was significantly higher in the pooled groups receiving RT (19%) as compared with the pooled groups not receiving

RT (6%). If the group with surgery only (3-year survival 9%) was compared with the group given preoperative RT without CT (3-year survival 21%) there was, however, no significant difference in survival (20).

Two Japanese studies favor the use of postoperative RT, one using historical controls (21) and one randomized trial (22). In a French randomized trial, however, comparing surgery with surgery followed by RT including 221 patients it was shown that postoperative RT (45–55 Gy, 1.8 Gy/fraction) did not affect survival after curative esophageal resection (23). This was further substantiated in a randomized study by Fok et al. (24). A high incidence of complications in the intrathoracic stomach (37%) and associated deaths in this study might have been related to the fractionation used (3.5 Gy/fraction, 3 fractions/week, total dose 49–52.5 Gy).

In conclusion, the addition of RT given pre- or postoperatively has not demonstrated any clear survival benefit as compared to surgery alone. The question whether surgery or RT alone should be used for primary local treatment is still unanswered.

Chemotherapy

In about 25% of patients with EC the tumor is loco-regional as defined by autopsy materials, even if autopsies were performed relatively soon after surgery (25–27). This may advocate the use of CT in EC. At least 12 chemotherapeutic drugs have been tested as single agents. Response rates over 20% can be calculated, when several trials are compiled, for five drugs: cisplatinum (20 responses/86 evaluable patients), methotrexate (23/67), mitoguazone (MGBG) (9/45), mitomycin-C (15/58) and vindesine (28/83) (1, 28–30). Of the responses, however, very few are complete remissions (CR) (28). Used as single agents doxorubicin, bleomycin, carboplatinum, CCNU, etoposide, ifosphamide, and 5-fluorouracil (5-FU) are less effective, but can still result in major responses in patients with advanced EC (28, 31–35).

The question whether multidrug combinations are of any benefit has not been enough addressed. There are preliminary data from one randomized trial comparing cisplatinum + 5-FU with cisplatinum alone in advanced EC showing a superior response rate for the combination (36% vs 11%) (36). The response to cisplatinum alone seems, however, somewhat low in comparison with presented single-arm studies (20 CR + PR in 86 treated patients) (1, 29). Various combinations including 2, 3 or even 4 drugs with different mechanisms of action have been used in phase II studies. It is apparent from Table 1 that cisplatinum has almost invariably been used as one part of different combinations. Response rates for combinations including cisplatinum have been in the range 31–76%. Since no randomized comparison has been performed it is not possible to say whether one cisplatinum-containing regimen is markedly superior to another. The figures for response rates presented in Table 1 represent a compilation of data from studies both on preoperative CT, including mainly patients with loco-regional disease, and on CT given to patients with advanced disease. The use of CT preoperatively makes any determination of response duration impossible. In patients with advanced disease response duration is usually brief, in the range of 2–6 months (67). Kelsen & Atiq (67) argued for a true response rate of 45–55% in patients with loco-regional disease and 25–30% in patients with advanced extensive disease for cisplatinum containing combinations. To ameliorate the therapeutic index, by avoiding side-effects of cisplatinum, the analog carboplatinum has been tested both as a single drug and in combination with vinblastine. The response rates for carboplatinum have, however, been low (31, 32, 37, 68) favoring the use of cisplatinum. At present further trials with carboplatinum are not warranted. The mitotic inhibitors taxol and taxotere, however, are new interesting drugs that need evaluation in EC.

Table 1

Combination chemotherapy

	No. of patients	Response rate[1] No. (%)	Ref.
Carb + Vinb[2]	16	0 (0)	37
Bleo + Adria	16	3 (19)	38
DDP + Bleo	140	43 (31)	39–43
DDP + VP16	43	20 (47)	44, 45
DDP + 5FU	202	94 (47)	28, 46–48
DDP + Ara-C	15	9 (60)	49–51
DDP + Mtx	42	32 (76)	30
DDP + VP16 + Bleo	16	5 (31)	28
DDP + Mtx + Bleo	41	13 (32)	52, 53
DDP + 5-FU + Adria	21	7 (33)	54
DDP + Vind + Send	28	10 (36)	55
DDP + Vind + MGBG	39	16 (41)	56
DDP + Vinb + MGBG	34	16 (47)	57
DDP + Vind + Bleo	192	91 (47)	58–62
DDP + 5-FU + Vind	22	12 (55)	55
DDP + 5-FU + Bleo	38	23 (61)	63
DDP + 5-FU + VP16	20	13 (65)	64
DDP + Flox + VP16	15	10 (67)	45
DDP + 5-FU + Mtx (+ Leuc)	34	24 (71)	65
DDP + 5-FU + Vinc + Bleo	10	6 (60)	28
DDP + Mtx + Bleo + MGBG	14	9 (64)	66

[1] Compilation of partial (PR) and complete responses (CR).
[2] Adria = doxorubicin (Adriamycin), Ara-C = cytosine-arabinoside, Bleo = bleomycin, Carb = carboplatinum, DDP = cisplatinum, 5-FU = 5-fluorouracil, Flox = floxuridine, Leuc = leucovorin, MGBG = mitoguazone, Mito = mitomycin-C, Mtx = methotrexate, Send = sendoxan, Vinb = vinblastine, Vinc = vincristine, Vind = vindesine, VP16 = etoposide

Compiled data (Table 1) suggest that the combination of cisplatinum with an antimetabolite like cytosine-arabinoside, methotrexate or 5-FU could give rise to high response rates. Combinations of two DNA-reactive agents like cisplatinum, bleomycin or doxorubicin seem less warranted (Table 1). It is tempting to speculate that a combination of a DNA-reactive agent like cisplatinum with an antimetabolite will result in an interaction by interference of the antimetabolite with DNA repair of cisplatinum-induced DNA lesions (69, 70). Another interesting approach to increase the response rate for CT might be the use of modulated 5-FU therapy. In two recently published studies in patients with advanced EC treated with 5-FU + IFN-α a response rate of around 25% was obtained (71, 72). The conclusion of Kelsen et al. (71) was that this response rate was similar to that reported for cisplatinum-containing combinations in similar patient populations. The data have, however, to be interpreted with some caution since there were no controls with 5-FU only.

Preoperative chemotherapy

The concept of preoperative CT has been explored with the rationale to attack systemic and local disease which cannot be removed by surgery. A compilation of trials where preoperative CT was given can be found in Table 2. Surgery was usually performed 1–4 weeks after completed preoperative CT (1–3 cycles). In the trials there are several different approaches to postoperative treatment. The effect of different cytotoxic agents in different combinations given preoperatively has resulted in pathologic complete remissions (P-CR) in about 2% of operated cases and overall response rates for CT of 40–50%. The mortality due to surgery does not seem to increase and the overall mortality related to treatment is around 7% (compiled out of the material in Table 2).

Three randomized trials comparing preoperative CT with surgery alone have been presented, neither one showing any significant survival benefit for patients receiving CT (20, 59, 77). Roth et al. (59) reported on 39 patients randomly assigned to receive either CT (cisplatinum + vindesine + bleomycin) and operation or operation alone. The median survival was 9 months for the two groups, corresponding to 27% vs 14% 2-year survival for preoperative CT and operation alone (extracted from survival curve). Patients responding to preoperative CT (47%) had significantly prolonged survival (median > 20 months) when compared with either non-responders (median 6.2 months) or the 'operation alone group' (median 8.6 months). Similar results have also been presented by Schlag et al. (77) reporting on 46 randomized patients (preoperative cisplatinum + 5-FU vs operation alone). Pa-

Table 2

Preoperative chemotherapy

	Patients No.	Operated[1] %	Resected[1] %	Response rate[2] No. (%)	P-CR[3] No. (%)	Survival % 1 yr	2 yr	5 yr
Single drug								
Bleo	19	—	53	5 (26)	0	26	21	—
DDP[4]	20	95	95	11 (55)	0	55	40	—
Two drugs								
DDP + 5-FU	61	74	61	31 (51)	1 (2.2)	65	42	31 [35]
DDP + Bleo	43	79	60	6 (14)	0	—	9[5]	—
Three drugs								
DDP[6]	202	81	69	97 (48)	5 (3.1)	56 [109]	34 [92]	—
Overall	345	79	67	150 (43)	6 (2.2)	56 [209]	36 [192]	31 [35]

[Number] = No. of patients included, if not all at risk. Abbreviations for drugs, see Table 1. For statistics, see Table 5.

[1] Percentage of all patients

[2] Response to CT (CR + PR)

[3] Pathologic CR as defined histologically, percentage of those operated

[4] DDP + Vinb (n = 3), DDP + 5 FU (n = 2)

[5] 3 yr survival, not included in compiled 2 yr figures

[6] Second cytotoxic agent = Vind or Vinb
Third cytotoxic agent = MGBG, Bleo, Send or 5-FU

References Single drug Bleo(73), DDP(74)
Two drugs DDP + 5-FU(46, 47 + 75), DDP + Bleo(76)
Three drugs DDP + Vind + 5-FU/Send(55)
DDP + Vind/Vinb + MGBG(56, 57)
DDP + Vind + Bleo(59 – 61)

tients responding to preoperative CT (50%) had significantly prolonged survival (median 13 months) compared with non-responders (median 5 months), but the median survival for the preoperative CT group and the surgery only group was identical (10 months) (77). These median survival times equal a 1-year survival of 18% vs 32% for preoperative CT and operation alone (extracted from survival curve). In this study, however, preoperative CT was associated with considerable side-effects (higher postoperative rate of septic complications and respiratory disorders combined with increased surgery related mortality) (77).

In a Scandinavian study (see above) preoperative CT (cisplatinum + bleomycin) was compared with preoperative RT, preoperative CT + RT and surgery alone (20). No statistically significant difference in survival was seen between preoperative CT (3-year survival 3%) and surgery alone (3-year survival 9%), but patients receiving preoperative RT (with or without CT) (3-year survival 19%) survived significantly longer than patients receiving CT alone before surgery (20).

The question whether CT or RT should be used preoperatively has been raised by Kelsen et al. (62) in a randomized comparison between preoperative CT (2 cycles of cisplatinum + vindesine + bleomycin) and preoperative RT (55 Gy, 1.8 Gy/fraction). The trial had a cross-over design which makes it impossible to analyze survival according to preoperative therapy. The response rate for CT was 55% and for RT 64%. According to the authors CT is as effective in treating local tumors as RT, which should be regarded as the message of this paper (62).

In conclusion, the compiled data speak for an advantage of preoperative cisplatinum based CT as regards short-term survival (2 years) compared with previously described treatment modalities. The three published randomized studies have, however, not been able to show any survival benefit for preoperative CT as compared with surgery alone. The relatively small number of included patients (20–50/treatment group) in all three studies might be a limitation when interpreting the data.

Preoperative chemoradiation

With the aim to potentiate RT and to treat disseminated disease, CT has been used concomitantly with RT before surgery. A compilation of data on preoperative chemoradiotherapy is presented in Table 3. The radiation dose given preoperatively was between 20 and 45 Gy usually in 2 Gy fractions and with few exceptions given concurrent with CT (1–3 cycles). Time to operation after completed preoperative treatment was usually in the range of 1–4 weeks. There is no uniformity regarding postoperative treatment in these studies. Based on compiled data (Table 3) a mean P-CR rate of 22% can be calculated for operated cases. This figure can be compared to results obtained with preoperative CT alone (P-CR 2%, see Table 2) and preoperative RT (25–66 Gy) alone (P-CR 7% in 563 operated

Table 3

Preoperative chemoradiation

	Patients No.	Operated[1] %	Resected[1] %	P-CR[2]	Survival %		
				No. (%)	1 yr	2 yr	5 yr
Single drug							
Bleo	141	61	51	—	28 [76]	18	—
Mtx[3]	93	59	59	15 (27)	—	—	—
DDP	117	95	86	24 (22)	49	—	—
Two drugs							
DDP + 5-FU	345	70	60	56 (23)	56 [259]	31	—
DDP + VP16	59	53	53	13 (42)	—	42	—
5-FU + Mito	63	92	89	14 (24)	53 [30]	33 [33]	15 [33]
Three drugs							
DDP + 5-FU + Mito	39	100	92	13 (33)	59 [17]	66 [22]	—
DDP + 5-FU[4]	70	76	70	13 (25)	52	45	34 [43]
Overall	927	73	65	148 (22)	49 [569]	32 [670]	26 [76]

[Number) = No. of patients included, if not all at risk. Abbreviations for drugs, see Table 1. For statistics, see Table 5.

[1] Percentage of all patients

[2] Pathologic CR as defined histologically, percentage of those operated

[3] Mean survival, resected patients, 26 months

[4] Third cytotoxic agent; Vinb (n = 43), vinc (n = 11) DDP + 5-FU alone (n = 11), 5-FU + Mito alone (n = 5)

References Single drug Bleo (73, 78), Mtx(79), DDP(80)
Two drugs DDP + 5-FU(81–88), DDP + VP 16(89)
5-FU + Mito(90, 91)
Three drugs DDP + 5-FU + Mito(92, 93)
DDP + 5-FU + Vinb/Vinc(94 + 95 + 96, 97)

patients, compiled from refs. 15, 16, 98–102) which may suggest a supraadditive effect between CT and RT. Since this is a new treatment approach it is not clear how to optimize the delivery of cytostatic drugs when used in combination with RT. There are some reports on the use of protracted 5-FU infusion for more than 5 days (94, 103–105) where the idea has been to prolong the exposure time in order to attack non-cycling or slowly proliferating tumor cells more effectively than with bolus administration. It is also possible that prolonged 5-FU exposure may inhibit the repair of radiation induced sublethal damage (106). Lokich et al. (104) reported on 13 patients with EC treated with prolonged 5-FU concurrent with RT giving a very high response rate, 10 clinical-CR (C-CR) and 2 P-CR. Encouraging results have also been obtained by Forastiere et al. (96) with the use of protracted 5-FU for 21 days concurrent with RT (37.5–45 Gy), however, with the addition of cisplatinum and vinblastine for two cycles during the treatment period, reaching a median survival of 29 months for 43 patients and a survival of 34% at 5 years.

Toxicity of concomitant preoperative CT and RT is substantial but, according to almost all authors, acceptable. The overall treatment-related mortality including surgery in concomitantly treated patients is around 9% (compiled out of the material in Table 3) which is comparable to pooled data from newer series on surgery alone (9).

There is one randomized trial using bleomycin alone comparing concurrent preoperative CT and RT (30 Gy, 1.5 Gy/fraction) with preoperative RT (35 Gy, 1.75 Gy/fraction). No benefit concerning survival was obtained with the addition of CT. The 2-year survival was 25% vs 19% for the combined preoperative therapy (CT + RT) and preoperative RT alone respectively (78). This is not surprising in view of the low level of activity seen with bleomycin in EC. As discussed earlier a randomized study including one treated arm with sequential preoperative CT (cisplatinum + bleomycin) and RT was recently published (20). No difference regarding survival comparing preoperative CT + RT (3-year survival 17%) with patients operated only (3-year survival 9%) was found (20). No randomized trial has been presented using preoperative combination CT and concurrent RT as compared to surgery alone. There is a need for such a study. Compiled results from studies on preoperative chemoradiotherapy indicates an increased short-term survival (2 years) for this modality, when multidrug combinations are used, compared to local treatment modalities only. Using historical control groups treated with surgery only two different authors also propose a survival benefit for patients treated with chemoradiotherapy followed by surgery (97, 108).

Chemoradiotherapy without surgery

Concomitant treatment by CT and RT may theoretically result in supraadditive antitumor effects. Data mainly from phase II trials on chemoradiotherapy without surgery are summarized in Table 4. The radiation dose used was usually 40–60 Gy in 2 Gy fractions given concomitantly with CT (usually two cycles). There are three published randomized trials comparing RT and RT plus a single cytotoxic agent (bleomycin or methotrexate) where no benefit from addition of CT could be established concerning survival (78, 109, 112). One problem with these studies might be that neither of the compounds (bleomycin or methotrexate), used as single agents, could be considered optimal when treating EC. Besides given concurrent, RT and CT may be administered sequentially. There is one recently published randomized study comparing sequential CT (cicplatinum + bleomycin) + RT (63 Gy, 1.75 Gy/fraction) with RT (63 Gy, 1.75 Gy/fraction) alone in patients with inoperable, localized EC. No benefit regarding survival or palliation, judged as swallowing function, was demonstrated by the sequential addition of CT in this case (122).

Another type of comparison has been made in two randomized trials by Kolaric et al. (38, 123). CT alone has been compared with CT (doxorubicin + bleomycin or doxorubicin alone) given concurrent with RT showing significantly better response rates when combined therapy was used (38, 123). In a first study the response rate was 33% vs 60% for doxorubicin and doxorubicin + RT (45–52 Gy, 2 Gy/fraction) respectively (123) and in a second study doxorubicin + bleomycin gave a response rate of 19% and doxorubicin + bleomycin + RT (36–40 Gy, 2 Gy/fraction) a 60% response rate (38).

There are interesting data from two randomized studies using combination CT concurrent with RT. In one study the combination of 5-FU + mitomycin-C + bleomycin was given concurrent with RT (50 Gy, 2 Gy/fraction) and compared with RT (50 Gy, 2 Gy/fraction) alone. The overall 5-year survival rates were 6% and 16% for the RT and CT + RT groups respectively (124). This difference did not reach statistical significance ($p = 0.16$) which might be related to the low number of patients ($n = 59$) entered in the trial. In another recently published report by Herskovic et al. (125) of a US intergroup study comparing CT (cisplatinum + 5-FU) + RT (50 Gy, 2 Gy/fraction) with RT (64 Gy, 2 Gy/fraction) alone the survival for the RT group at 1 and 2 years was 33% and 10% respectively and for the CT + RT group 50% and 38% ($p < 0.001$). The patients who were treated with CT + RT had fewer local ($p < 0.02$) and fewer distant ($p < 0.01$) recurrences (125).

Interim analysis of two ongoing randomized studies also favor a CT-containing approach (126, 127). For patients with loco-regionally advanced EC preliminary results from one trial with 84 included patients show prolonged survival in the group treated with CT (cisplatinum + 5-FU) concurrent with RT (40 Gy) (12+ months median survival) as compared with the group treated with RT (60 Gy) alone (6+ months median survival) ($p = 0.0486$) (126). These results are further strengthened by an interim analysis of a

Table 4

Chemotherapy/Radiotherapy

	Patients No.	Response rate[1]		Survival %		
		No.	(%)	1 yr	2 yr	5 yr
Single drug						
5-FU[2]	6	5	(83)	—	—	—
Bleo	104	54	(52)	26 [64]	12 [40]	—
Mtx	78	—		31	15	7.7
Two drugs						
DDP + 5-FU	71	51	(72)	59 [46]	37	—
DDP + VP16	34	—	—	50	—	—
5-FU + Mito	131	71 [96]	(74)	59 [86]	35 [86]	32 [30]
Bleo + Adria	15	9	(60)	27	—	—
Three drugs						
DDP + 5-FU + Mito[3]	62	32 [42]	(76)	55	25	—
DDP + 5-FU + Mtx[4]	9	8	(89)	—	—	—
Bleo + Vinc + Mtx	26	21	(81)	48	21	—
Overall	536	251 [369]	(68)	45 [411]	26 [363]	14 [108]

[Number] = No. of patients included, if not all at risk. Abbreviations for drugs, see Table 1. For statistics, see Table 5.

[1] Response to CT + RT

[2] Median survival time + 6 months

[3] Bleo also included (n = 16)

[4] Median survival time 7 months

References Single drug Bleo (78, 109, 110), 5-FU(111), Mtx(112)
Two drugs DDP + 5-FU(46, 84, 113), DDP + VP16(114)
5-FU + Mito(90, 115–117), Bleo + Adria(38)
Three drugs DDP + 5-FU + Mito(92, 118, 119)
DDP + 5-FU + Mtx(120), Bleo + Vinc + Mtx(121)

randomized study performed by Sischy et al. (127). The analysis included 118 eligible patients and compared RT (60–64 Gy) with chemoradiation (60–64 Gy, 5-FU + mitomycin-C). The median survival was 9.0 months for RT alone and 14.9 months for patients treated by chemoradiotherapy (p = 0.03) (127). The study allowed an option for surgical resection after 40 Gy but data presented from an initial analysis showed no improvement in median survival by addition of surgery in patients receiving chemoradiotherapy (13.7 months with resection vs 14.8 without) (128). This lack of increase of survival by addition of surgery instead of RT after initial treatment with CT + RT is also reported in another recent publication (129). Thus, the results of chemoradiation (combination CT given concurrent with RT) are promising and results of 5-year survival in the randomized materials will be interesting for future guidelines in the treatment of EC.

Conclusions and suggestions for further studies

The majority of EC patients suffer from disseminated disease already at diagnosis. Treatment modalities, such as surgery and/or RT, will therefore only be able to cure a fraction of the cases, e.g. those with localized disease. The survival figures for surgery or RT alone, 5–10% at 5 years (Table 5), show that these modalities may not even provide optimal local control. Unfortunately, as pointed out before, no randomized comparison has been made between RT alone and surgery alone in localized EC. We doubt, however, that such a study will ever be performed, albeit, it would have been very important.

The use of preoperative RT has only been evaluated in a randomized manner in a few studies but these data do not support a role for preoperative RT with the radiation doses that have been given in these studies (20–45 Gy). Higher radiation doses in a preoperative setting may compromise surgery and has probably therefore not been systematically tested. For postoperative RT there are less data presented which makes the possible benefit even harder to evaluate. Two published randomized trials were not able to show any positive effect on survival by addition of RT (45–55 Gy) after surgery.

The inclusion of CT into local treatment modalities, surgery and/or RT for primary treatment has been extensively tested in phase II studies during the last decade. The results of these studies give room for some optimism. Compiled data indicate higher 1- and 2-year survival figures as compared with surgery or RT alone (Table 5). One problem is that very few randomized studies using adequate CT have been carried out as yet. Randomized

Table 5

Compiled treatment results

Reference	Treatment modality	Patients No.	Comments	Survival %		
				1 yr	2 yr	5 yr
5	Surgery alone	83 783	Op 58% (24), Res 39% (22)	18 (13)	9 (7)	4 (3)
			Operated patients	31	14	9
11	Radiation alone	8 489	Palliative 51%	18 (7)	8 (6)	6 (6)
**	Radiation alone	2 040	Curative intent	35 (12)	17 (8)	7 (4)
***	Preop radiation	1 573	Op 93% (14). Res 71% (17)	41 (15)	21 (10)	14 (13)
Table 2	Preop chemotherapy	345	Op 79% (14), Res 67% (17)	56 (14)	36 (9)	*
Table 3	Preop chemoradiation	927	Op 73% (20), Res 65% (23)	49 (19)	32 (16)	*
Table 4	Chemoradiation	536	Mainly inoperable cases	45 (19)	26 (13)	*

* Sufficient data not presented.
** References: 10, 12, 13, 130–136
*** References: 15, 16, 18, 19, 78, 98–102, 132, 134, 136–140
Statistics: Survival was calculated by dividing the total number of patients reported as alive by the total number of patients included in the studies from which survival figures were extracted. Standard deviation (s.d.) was calculated from the survival percentages extracted from the single reports. The same type of calculation was performed for the figures for operated (Op) and resected (Res) cases.
Compiled data; % (s.d.)
References 5 and 11; mean % (s.d.)

studies with sufficiently long follow-ups are warranted to define the role of CT in curative attempts in EC. Several large randomized studies using adequate combination CT regimens are under way, both assessing preoperative CT and preoperative chemoradiotherapy (141).

Due to the toxic character of multimodality treatments, especially those including CT, it seems important to evaluate quality of life aspects in forthcoming studies. The vast majority of patients with EC will have a disease that is probably not curable. With this in mind a careful selection is needed even before allocating a patient to a study protocol or to the standard treatments (surgery/RT). The use of endosonography in combination with ordinary x-ray investigations and computer scans are of utmost importance for staging and to enable comparison of different studies. Well-performed studies may give guidelines for the selection of patients for primary curative as opposed to palliative treatment.

There are not many studies focusing on adjuvant CT as opposed to neoadjuvant treatment. In a Japanese randomized study the concept of postoperative RT or CT (cisplatinum + vindesine) was tested without any significant difference in survival at 5 years between the two groups (142). Adjuvant therapy, however, may not necessarily implicate CT only. About half of the cases will be responders to CT but only a fraction will be P-CR. Thus, a substantial part of the cancers will at least conceptually have some component which is CT resistent. One may therefore advocate non CT agents, such as biological response modifiers, as adjuvant therapy. Examples may be interferon and retinoic acids which have shown antitumor effects in SCC of the skin and head and neck (143–145).

In conclusion, today there are not enough data to support CT as part of a standard treatment of EC. Treatment results mainly from studies utilizing combination CT given concurrent with RT give room for some optimism but surgery or RT should still be regarded as standard treatment modalities except for in controlled trials.

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