Preoperative chemoradiotherapy in esophageal cancer

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Esophageal cancer is a challenging clinical problem. Despite surgical advances and use of combined-modality approaches, the prognosis remains dismal. According to the EUROCARE-3 study (1990-1994), the overall European 1-year and 5-year relative survival rates were 33% and 10%, respectively[1] and a plateau in survival following single modality treatment has been reached.

Natural history of esophageal cancer

Esophageal cancers have extensive local growth and early lymph node involvement before widespread dissemination. Interconnexions between lymphatic channels of the esophagus provide a submucous passway for the lymphatic dissemination of cancer. Viable tumor emboli can be found sometimes as much as 8 cm distant from the primary cancer. The disease causes death by both local growth and distant metastases[2-6]. Lymph node involvement is documented in 61-74% of patients. Distant metastases have been noted in virtually every tissue, including lymph nodes, lungs, liver, adrenals, stomach, bones and kidneys.

Surgery

Locoregional control is a major aim in curative management of localized carcinoma of the esophagus. Both surgery and radiotherapy have been used with modest survival outcomes. No well-designed randomized controlled trial was performed to determine which treatment (primary surgery or primary radiotherapy) is superior. Those who advocate surgery emphasize the good survival rate for small tumors (T1 or T2 N0) and the quick relief of dysphagia.

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However, a critical review of surgery done by Earlam et al[7] revealed from the study of 122 series with 83,783 patients that the survival rate was 4%, with an operation rate of 58%, resection rate of 39% and a resection mortality of 29%. In the MD Anderson Cancer Centre Experience[8], the median survival has doubled during the period 1970 to 2001. However, in patients treated with surgery alone, no change in survival with time was noted for patients having the same postoperative pathologic stage. In a recent American series, hospitals that perform a large number of esophagectomies (5 cases or more per year) have a decreased post-operative mortality (4% versus 13%) and a decreased length of stay[9]. However the 5-year survival rate seldom exceeds 25%.

Most surgeons remove a minimum of 8 cm of esophagus proximal and distal to the tumor. This most often requires a near total esophagectomy. Akiyama et al[10] have advocated a radical (en-bloc) three-field lymphadenectomy, including the intrathoracic, intra-abdominal and cervical nodes. Few surgeons have experience with this technique. Randomised controlled studies are necessary to find out if extended lymphadenectomy leads to a therapeutic benefit. According to the UICC, a minimal number of six mediastinal nodes should be dissected for optimal staging.

Different surgical techniques are used; none are considered to be ideal for all tumors and the procedure is chosen depending on the location of the tumor, the extent of resection, the patient's performance status and the experience of the surgeon. Right thoracic procedures (Ivor-Lewis, also called Lewis-Tanner) allows dissection of the nodes at the abdominal and thoracic levels when the tumor is located under the aortic arch. Transhiatal esophagectomy does not require a thoracotomy but cannot permit the dissection of sub-carinal nodes and some authors consider this procedure as palliative.

However, four randomized studies did not find a statistically significant survival difference between transhiatal and transthoracic approaches. In the more recent trial[11] including 220 patients, transhiatal esophagectomy was associated with a lower morbidity than transthoracic esophagectomy, but a trend towards improved long-term survival was observed with the extended transthoracic approach. Despite no agreement on a standard surgical technique, surgery is still the mainstay of therapy for localized resectable esophageal carcinoma.

Preoperative radiotherapy

Five clinical trials including 107 to 326 patients addressed the role of a preoperative radiotherapy. Doses varied from 20 Gy to 40 Gy, but even in the trial with the higher doses, the fractionation was far from optimal (40 Gy in eight fractions). A meta-analysis on 1,147 patients was performed and has shown a 11% reduction in mortality (confidence interval 95%: 0.78-1.01), p = 0.062 (12). The benefit is limited to 3% increase in survival at 5 years.

Preoperative chemotherapy

The rationale for use of preoperative chemotherapy includes an attempt to eliminate micrometastases and to decrease the size of the primary tumor, thereby increasing the surgical resection rate. Early trials comparing neoadjuvant cisplatin-based chemotherapy did not demonstrate any survival advantage[13-17]. However, these trials included a limited number of patients, (n = 36-147). More recently, the American Intergroup trial[18] compared neoadjuvant cisplatin and 5-FU for three cycles versus surgery alone in 423 patients and failed to reveal any survival difference. Two other trials showed conflicting results. Dutch investigators[19] used an etoposide and cisplatin combination. A statistically significant improvement in survival was demonstrated versus transhiatal surgery alone. The second trial was performed by the MRC[20] and has recruited 802 patients with squamous cell (34%) or adenocarcinoma (66%). Patients in the preoperative chemotherapy arm received two courses of cisplatin and 5-FU. No guidelines for surgery were given in this trial and 10% of the patients received also radiotherapy. An increase in R0 resection and a 9% increase in three-year survival rate was shown. Improvement in overall survival was demonstrated, but not in the subgroup of squamous cell esophageal carcinomas. Further trials in this area are needed to clarify the issue.

Definitive chemoradiotherapy

Eight studies comparing chemoradiotherapy (CRT) to radiotherapy had been published. The most recent trials used a combination of cisplatin and 5-FU. In the RTOG study 85-01[21], two courses of chemotherapy during 50 Gy radiation therapy (followed by additional two courses of the same chemotherapy) versus 64 Gy radiotherapy alone were investigated. No patient survived at three years in the radiotherapy group but 26% of the patients in the CRT group were surviving at 5 years. A substantial reduction in local recurrences after CRT was demonstrated. However, this was at the expense of a higher risk of grade 3-4 toxicities. Major toxicities occurred in 20% of the patients and only 60% of the patients can tolerate the full treatment. Long-term survival benefit was confirmed by an ECOG study using 5-FU and mitomycin C[22]. According to a second randomized RTOG study, the increase of radiotherapy dose up to 64.8 Gy is no more efficient than 50 Gy when concomitant chemotherapy is administrated. The higher dose is associated with a higher rate of toxic death, 9% versus 2%[23]. The results of CRT for patients with adenocarcinoma of the oesophagus appeared comparable to those obtained in squamous cell carcinoma, with a 2-year survival of 14-36%. In patients with good performance status, CRT is now the treatment of choice when surgery is not applicable.

Preoperative chemoradiotherapy

Triple modality therapy has emerged in an effort to maximize the local control. More than 50 non-randomized studies have been published with pathologic complete responses (pCR) ranging from 8 to 56%. The operative mortality rate was around 10%. A 60% 5-year survival rate was observed in case of pCR. No major difference appeared between squamous cell carcinoma and adenocarcinoma.

Eight randomized studies comparing preoperative CRT to surgery alone have been reported (Table I). Three studies[15, 24, 25] were reported before 1995 and have included a limited number of patients. Three recent randomized studies are of major interest. The Dublin study involved only patients with adenocarcinoma[26]. Staging was suboptimal (optional CT-scan, no endoscopic ultrasonography). Patients (n = 113) were to receive either surgery alone or two courses of neoadjuvant chemotherapy (cisplatin/5-FU) with concurrent radiotherapy (40 Gy). Eleven patients were withdrawn for protocol violations. Five different surgical techniques were used, indicating probably a large heterogeneity in tumor location. A statistically significant survival benefit was noted for the CRT arm with a median survival of 16 months versus 11 months (p = 0.01). Survival curves have been presented excluding

TABLE I

Randomised trials of preoperative CRT versus surgery (s) alone in resectable esophageal cancer

First author (reference)	N_0	Adeno	Radiotherapy Gy	Fraction	Chemotherapy	pCR	Operative mortality (CRT arm)	Median survival (months) CRT	S	p
Nygaard[15]	88	0 %	35	20	CDDP/Bleo	ns	24 %	7	6	0.3
Apinop[24]	69	0 %	40	20	5-FU/CCDP	20 %	12 %	9.7	7.4	0.4
Le Prisé[25]	77	0 %	20	10	5-FU/CCDP (sequential)	10 %	8 %	10	11	0.6
Walsh[26]	113	100 %	40	15	5-FU/CCDP	22 %	10 %	16	11	0.01
Bosset[27]	282	0 %	37	10	CDDP (sequential)	20 %	12 %	18.6	18.6	0
Urba[28]	100	75 %	45	30	5-FU/CDDP vinblastine	28 %	2 %	16.9	17.6	0.15
Burmeister[29]	256	61 %	35	15	5-FU/CDDP	15 %	4.6 %	21	18	0.38
Lee[30]	123	0 %	45.6	38	5-FU/CDDP	21 %	ns	28.2	27.3	0.67

in-hospital deaths and patients with protocol violations. Moreover the 3-year survival was unusually poor in the surgery alone arm (7%).

The study from the University of Michigan[28] randomized 100 patients (75 adenocarcinomas, 25 squamous cell carcinomas) to surgery alone and neoadjuvant CRT (45 Gy/1.5 Gy bid/3weeks, using a cisplatin/continuous 5 FU/vinblastine regimen). Surgery was transhiatal esophagectomy. Local recurrence was decreased by half in the combined-modality group (19% vs 42% respectively, p = 0.02). No significant difference in 5 year-survival was seen. An Australasian trial randomized 256 patients (61% adenocarcinomas) between surgery and preoperative CRT (29). A radiotherapy dose of 35 Gy was delivered in 15 fractions during three weeks, together with two courses of cisplatin plus continuous 5-FU. The pCR rate was significantly higher for patients with squamous cell carcinoma than for adenocarcinomas. Median survival was 18 months in the surgery arm and 21 months in the combined-modality approach (ns).

The larger trial (297 patients) was performed by FFCD and EORTC investigators[27]: patients with squamous cell carcinoma were randomized between surgery alone and preoperative split-course radiotherapy (18.5 Gy in 5 fractions, 2-week gap, and then 18.5 Gy in 5 fractions) with two cycles of cisplatin alone. An increase in postoperative mortality rate was seen in the multimodal treatment as compared to surgery alone (12% vs 4%; p = 0.01). The median survival was the same in the two groups: 18.6 months. However, deaths due to esophageal cancer were significantly reduced in the combined modality group (68% vs 86%; p=0.002). Several factors may explain why this study did not find preoperative regimen to benefit patients in terms of prolonged survival: the deleterious effect of a high dose per fraction of radiotherapy (3.7 Gy compared with conventional fraction of 1.8-2 Gy), the break of 2 weeks between the two courses of 18.5 Gy and the use of cisplatin as single agent.

A meta-analysis including 9 studies concluded than CRT improves R0 resection rate, 3-year survival but a trend to increase treatment mortality after preoperative CRT was also described[31]. However, this meta-analysis was performed from published trials and not from updated individual patients data. Further trials in this area are needed.

Optimal CRT combinations and high-quality delivery are essential to any routinely used strategy. Modern radiotherapy CT planning techniques and a critical evaluation of target volume definitions should all contribute to lower morbidity. A recent meta-analysis of 46 trials including 1,335 patients[32] indicated that the pCR rate increases with the radiotherapy dose (p = 0.006). Conversely, an increase in radiotherapy duration decrease the pCR rate (p = 0.035). A clear dose-response relationship was demonstrated for both 5-FU (p = 0.003) and cisplatin (p = 0.018).

Due to the demonstrated increase of postoperative death, preoperative CRT cannot be now considered as the standard of care. So the EORTC with the FFCD launched a study (40001-22001) comparing preoperative CRT versus surgery alone in stage I-II squamous cell carcinoma and adenocarcinomas of the thoracic esophagus, using an optimized radiotherapy technique (45 Gy; 1.8 Gy per fraction, megavoltage radiation ≥ 6 MV, CT-based treatment planning, 3-4 fields technique, quality control procedures) with two courses of concurrent cisplatin-5-FU. Surgery consists of subtotal esophagectomy with abdominal and thoracic routes and two field lymph nodes dissection. The aim of this study is to demonstrate a 15% survival advantage at 3 years with the combined-modality treatment. More than 100 patients are already included.

Is surgery essential?

Several investigators have demonstrated that definitive CRT alone in localized esophageal cancer can result in survival rates similar to those of surgery alone[21]. Moreover, in the ECOG trial[22], there was no difference between CRT alone (median survival: 17 months) and CRT followed by surgery (median survival: 11 months). Taking into account the postoperative mortality rate of surgery and its costs, the addition of surgery following CRT can only be justified if it still confers an improvement in overall survival when compared to patients treated with CRT alone. This question has been addressed by two trials, FFCD 9102 and a recent German trial.

In the FFCD trial, 444 patients with operable T3 cancers were first treated with CRT (46 Gy + two courses of 5-FU/cisplatin). Responding patients (n_0 = 259) were randomised between surgery or completion of CRT. No difference in survival appeared between the two arms. However, patients treated with CRT had significantly more esophageal strictures needing dilatation or stent (46% versus 24%; p < 0.005). Mortality at 3 months was increased in the surgical arm (9.3% versus 0.8%; p < 0.005). The duration of hospital stay was also longer in the surgery arm. Quality of life was measured with the Spitzer index. At the first follow-up, quality of life scores were higher in the CRT arm but long-term quality of life was similar in the two arms. The conclusion of this trial was that patients having a locally advanced cancer and responding to induction CRT had the same survival and quality of life whether they had surgery or not[33, 34].

A second trial addressed the role of surgery in patients with T3-T4 thoracic squamous cell carcinoma[35]. One hundred and eighty-four eligible patients were included but only 172 were randomized and at ASCO 2003 presentation, the results include also 12 patients treated without randomization (7 chose arm A and 5 arm B). All patients received 3 cycles of preoperative FLEP (5-FU, leucovorin, etoposide, cisplatin). Then patients were randomized between continuation of CRT to 66-70 Gy with concomitant etoposide plus cisplatin, and 40 Gy plus etoposide/cisplatin followed by transthoracic esophagectomy. Overall treatment-related mortality was 7.6%, including 2.3% toxic deaths during chemotherapy and 12.3% postoperative deaths. Among patients randomized to CRT alone, 5 had surgery and an additional 5 patients out of 12 treated without randomization underwent surgery. Overall, the resection rate was 62%. For all patients except 4, an R0 resection was achieved. Local control at 3 years was better in the surgical arm. However, no difference in survival appeared between CRT and surgery, but surprisingly survival curves also included the 12 patients treated outside of the protocol. However, this trial seems to confirm the equivalence in survival between the surgery and the no-surgery groups.

To conclude, CRT has been proven superior to radiation alone, but preoperative CRT is still an investigational approach. All clinicians are encouraged to enter patients in clinical trials to provide improvement in curability and quality of life for patients with esophageal cancer.

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