The Value of Preoperative Radiotherapy in Esophageal Cancer: Results of a Study of the E.O.R.T.C.


Attempts to combine radiation therapy and surgery in patients with operable carcinoma of the esophagus began 30 years ago. The first reported surgical series showed a low rate of resectability and a high postoperative mortality. Results of radiation therapy alone were also disappointing in the long run, especially in patients who appeared to be excellent operative risks with small localized tumors. The rationale for a combined approach was that x-ray therapy could bring about a reduction of tumor activity and bulk, an improvement in nutritional state through the restoration of the ability to swallow, a reduction of transplantability of the tumor, and a curative effect on periesophageal regional disease which is not treated well by surgery. On the other hand, surgery often allowed an extended resection, clearing residual foci or distant esophageal wall extension. The limit of a combined approach is the toxicity of the preoperative radiation which must be mild enough to allow surgery to proceed without excessive delay or increased mortality. Numerous radiotherapy schedules were tried using different fields, doses, and fractionations, most of them in nonrandomized studies. Two prospective randomized trials have been recently reported. The final results of a third prospective trial, run by the E.O.R.T.C., will be presented.

Historical Studies

Comparative analysis of historical studies (Table 1) is made difficult by the frequent lack of data concerning the staging of the tumor, the delay between radiation and surgery, the toxicity and the morbidity of radiation, and the number of patients at risk for long-term evaluation.

The first studies [1, 2] used long-term fractionated radiation, about 45 gray (Gy) in 4 weeks, with surgery having been performed after a 4-8-week period (or longer) of recovery. High doses (up to 50-60 Gy) were tested in Stanford, and by Akakura, but led to an unacceptable toxicity (12% lethality) [3]. The analysis of available reports (Table 1) shows that surgery had to be cancelled in as many as 50% of irradiated patients. In most series, however, the staging and the evaluation of operability were made at the end of the radiation period, not before.

Complications related to radiation necrosis (hemorrhage, perforation, fistula) have been reported. Radiation pneumonitis in 5% of survivors was only mentioned in the series of Marks et al. [4]. A different approach, consisting of a short-term concentrated radiation, was advocated by Nakayama on the basis of its high antitumor effect observed in mice [5]. Surgery was performed after a few days. This method was not used frequently, except in Europe where it was usually administered in 10 fractions for 12 days [6, 7].

Five studies (Table 1: Goodner, Doggett, Parker, Marks, Kelsen) reported that esophageal resection could be performed in 37.7% (254/673) of the preoperatively irradiated patients, or in 75% (254/338) of patients submitted to surgery. Akakura et al. reported a resectability rate of 82% (96/117) after radiotherapy, compared to 39.5% in a former control group, but these results point to the need for confirmation in prospective trials. Severe adherences around the cancer owing to connective fibrosis were encountered after 50-60 Gy radiation [8].

In the recorded data, the mean rate of postoperative deaths was 12.5% in operated patients and 14.5% in resected patients. Great disparities exist between the series: the mortality rate was 22.5% in resected patients from Western studies, most of them early studies, whereas it was only 4-6% in 2 Japanese studies [5, 9]. These rates were not different from those observed for surgery alone at the same time in the same countries. Radiation doses beyond 50 Gy [3, 8] were, nevertheless, followed by increased mortality (21% for Akakura versus 13% in the control group). Pulmonary complications were more frequent in preoperatively irradiated patients [9].

A beneficial effect on dysphagia and esophagogram was noticed in several studies, but a precise evaluation could only be made on resected specimens [10]. In Western studies using 40-50 Gy, the complete response rate was about 10%. Japanese studies showed that a high rate of markedly effective responses correlated to radiation dosage: 49/96 after 50-60 Gy [8], 16/49 after 40 Gy [11], and 15/104 after 25-30 Gy [9]. Compared with control groups, less infiltration of adventitia and resected
Table 1. Preoperative radiotherapy—historical studies.

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Interval</th>
<th>No. of treated patients</th>
<th>No. of operable patients</th>
<th>No. of resectable patients</th>
<th>Operative mortality (No. of patients)</th>
<th>Complete response (No. of patients)</th>
<th>Alive at 2 yr (No. of patients)</th>
<th>Alive at 5 yr or survival rate (No. of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doggett et al. [3] (prior to 1970)</td>
<td>50–60</td>
<td>4–6 wk</td>
<td>42</td>
<td>29</td>
<td>24</td>
<td>8b</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Akakura et al. [8] (1963–1968)</td>
<td>20–25</td>
<td>3–5 days</td>
<td>117</td>
<td>96</td>
<td>20b</td>
<td>49</td>
<td>-a</td>
<td>25% of patients at risk; no. of patients at risk not stated in literature</td>
</tr>
<tr>
<td>Parker et al. [16] (1967–1975)</td>
<td>45</td>
<td>1–8 wk</td>
<td>-a</td>
<td>-a</td>
<td>75</td>
<td>14b</td>
<td>10</td>
<td>-a</td>
</tr>
<tr>
<td>Kelsen et al. [22] (1965–1979)</td>
<td>40–60</td>
<td>2–4 wk</td>
<td>76</td>
<td>66</td>
<td>41</td>
<td>8</td>
<td>-a</td>
<td>-a</td>
</tr>
</tbody>
</table>

a Not stated in the literature.
b Resected cases.
c 20 Gy × 5 days in 19 patients.

Table 2. Preoperative radiotherapy—prospective studies.

<table>
<thead>
<tr>
<th>No. of patients included</th>
<th>Dose (Gy)</th>
<th>Interval</th>
<th>No. of operable patients</th>
<th>No. of resectable patients</th>
<th>Operative mortality (No. of patients)</th>
<th>Complete response (No. of patients)</th>
<th>Alive 5 yr or survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Launois et al. [6] (1973–1976)</td>
<td>67</td>
<td>39–45</td>
<td>&lt;8 days</td>
<td>62</td>
<td>47</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>8–12 days</td>
<td>-</td>
<td>47</td>
<td>33</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>Huang et al. [18] (1977–1982)</td>
<td>83</td>
<td>40</td>
<td>2–3 wk</td>
<td>83</td>
<td>79</td>
<td>3</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>77</td>
<td>4 wk</td>
<td>-</td>
<td>77</td>
<td>69</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>E.O.R.T.C. (1976–1982)</td>
<td>102</td>
<td>33</td>
<td>&lt;8 days</td>
<td>97</td>
<td>75</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>106</td>
<td>12 days</td>
<td>-</td>
<td>106</td>
<td>87</td>
<td>19</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
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<td>-</td>
<td>-</td>
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<td>-</td>
</tr>
</tbody>
</table>

* Postoperative survival.

Stumps, and less mediastinal lymph node involvement were noted by Akakura et al. Long-term survival was significantly better in responders, but this observation is known to be potentially subject to selection bias.

Survival results were disappointing. The 37.5% 5-year survival rate in resected patients assessed by Nakayama et al. was based on only 8 patients at risk, and the last report indicated a 5-year survival of only 15.8% [12]. In the literature, 4.6% of all patients were alive at 5 years: 10.5% of operated patients and about 15% of resected patients. The question is whether combined treatment is better than surgery alone: an improved survival rate of 25% versus 13.5% was reported by Akakura et al. over 2 consecutive time periods, whereas other simultaneous studies offered identical [9] or even worse [13] results. A better survival experience in Rotterdam [14] could be due to a high proportion of females (one-third) in that series. Concentrated radiation appeared to be better in the series of Kelsen et al., but in a small sample. Distant progression was common [3, 15] and more frequent in irradiated patients, contrary to local recurrences which were less frequent [8]. Overall, long-term results of the combined treatment appeared to be better than radiation alone in a priori operable patients [4, 14, 16].
Prospective Studies

In the French study (Table 2) [6], a high dose of concentrated radiation was applied before surgery in 67 patients, whereas 57 received surgery alone. There was no difference between the 2 groups of patients, either in resection rate or in operative mortality (22.5% versus 33.5% in the control group). The pretreatment clinical staging in the 2 arms was not specified (10 of the 57 patients in the control group did not undergo surgery). Excluding postoperative deaths, long-term survival was identical. The mean survival following an exploratory procedure was better in the control group (8.2 months versus 4.5 months) suggesting that this intensive regimen may have contributed to the unusually short survival in the combined modality patients [17].

The Chinese study [18] concerned 2 groups of 83 (pretreated) and 77 patients. Radiation was delivered in 10 fractions over 4 weeks, and surgery performed after a rest interval of 2–3 weeks. Operative mortality was low. Resectability rate was not significantly modified. The rate of lymph node metastases was 21.5% in irradiated patients versus 30.4% in the control group. Although the anastomotic site was within the field of preoperative radiation in half of the cases, the incidence of anastomotic leakage was not higher than that of the group treated by surgery alone. No information was available on the long-term survival of the whole group and the slight improvement at 5 years in the combined modality group was not significant.

The E.O.R.T.C. Prospective Study

Material and Methods

This prospective randomized trial was conducted by 8 European institutions known as the European Organization for Research and Treatment of Cancer (E.O.R.T.C.; see Acknowledgments). Criteria of eligibility were patients of both sexes, with a squamous cell carcinoma of the esophagus located at least 20 cm from the dental line, with no previous treatment for the lesion or other synchronous cancers, without presumed visceral metastasis, and without presumed mediastinal involvement such as laryngeal palsy or tracheobronchial invasion (T1–T2 according to the American Joint Committee for Cancer Staging). Some tumors with mediastinal extensions, T3, but without invasion of adjacent visceres were included. The preoperative evaluation included a complete clinical examination with special attention to weight loss and general condition as measured by the Karnovsky index. Patients with morbid disease such as senility, severe pulmonary insufficiency or infection, cardiac abnormalities, hepatic damage, impaired renal function, or severe malnutrition (weight loss of 20% of ideal body weight) were excluded. Radiological evaluation included x-ray esophagogram and computed tomographic (CT) scan or ultrasonography of the liver. Endoscopic evaluation required an esophagoscopy, a laryngoscopy, and a bronchoscopy if the lesion was located 20–35 cm from the dental line. Thoracic CT scan, azygography, bone scan, and laparoscopy were optional. Radiotherapy was performed in 10 fractions during 12 days up to a total dose of 3,300 rad, by linear accelerator. Two anterior and posterior fields were used on a mediastinal volume including 5 cm of the esophagus above and below the tumor. Whatever the arm of the study, patients were submitted to an intensive preoperative preparation, including nutritional support by enteral route in as many patients as possible. Special attention was given to dental care and thoracic physiotherapy. Surgery was performed within 8 days after the completion of radiotherapy. A one-stage procedure was recommended. The esophagus was resected at least 5 cm apart from the tumor margin, and lymph node dissection to celiac, paraatracheal, and paraesophageal regions was routinely carried out. The esophageal replacement was done with stomach or intestinal interposition. Tumors located above the aortic or azygos arch required a subtotal esophagectomy with cervical anastomosis. After surgery, patients were stratified in curative or palliative cases. Resection was considered curative if there was no macroscopic or microscopic evidence of residual tumor (including biopsies of adhesions) in celiac and mediastinal areas, and no evidence of invasion of the proximal esophageal stump. The trial was initially intended only for patients with a so-called curative resection. Because of the high rate of unpredictable palliative resections, all the randomized patients were kept on trial and followed up carefully every 3 months the first year, and every 6 months thereafter. Survival curves and disease-free curves were calculated from the date of randomization and were compared using the log-rank test.

Two hundred twenty-nine patients were randomized in 2 groups: group 1, 115 patients receiving preoperative radiation; group 2, 114 patients receiving surgery alone. Of the 229 patients, 15 were ineligible because of inadequate staging prior to randomization [8 in group 1 (XRT-surgery), 7 in group 2 (surgery alone)]. The reasons for exclusion were extra-esophageal spread in 9, associated cancer in 1, inaccurate preoperative biopsy in 3, and associated disease in 2. Two other patients did not receive the planned radiotherapy, and no data were available in 4 cases. The remaining 208 patients were fully evaluable: 102 in group 1, 106 in group 2. There were 199 men and 9 women, median age was 55 years (range: 33–73). The tumor staging and the tumor level were similar between the 2 groups (Table 3).

Results

Tolerance to radiotherapy was reported as good in 87 patients, moderate in 9, and bad in 3. Four patients had progression or
complications during radiotherapy (2 mediastinal fistulas, 1 digestive hemorrhage leading to death, and 1 severe esophagitis). The median time between the end of the radiotherapy and surgery was 4.8 days (range: 2-17). Five patients were not operated on at all: all of them had received radiotherapy (2 refusals, 2 progressions, 1 esophagitis). Two hundred and three patients were operated on (Table 4). No resection was performed in 41 patients with local or distant extension (20%). Fifty-three patients (26%) underwent a resection considered palliative by the surgeon. The resection was considered as curative in 109 cases (54%). There was no difference between the 2 treatment arms in terms of resectability or curativity. Of the 162 resected patients, a one-stage procedure with gastric transposition was used in 160, coloplasty in 1, and a two-stage procedure in 1. The anastomosis was intrathoracic in 116, cervical in 46. Among the 41 nonresected patients, a bypass procedure was performed in 14, and endoprosthesis in 2. The postoperative mortality (calculated within the whole hospital stay) was similar in both treatment arms (17% in nonresected cases, 32% after palliative resection, and 17.4% after curative resection) (Table 4). The median postoperative stay (22 days) and the causes of postoperative deaths (6 pulmonary complications in group 1 versus 8 in group 2) did not differ between the 2 treatments.

The pathological analysis of resected specimens showed no significant difference between the 2 treatment arms with regard to lymph node invasion or penetration of the tumor (Table 5). In the group receiving radiotherapy, 2 superficial tumors had been sterilized while 10 patients had a modified irradiated epithelium. The rate of lymph node invasion was 56% and 58.2%, respectively.

After a mean follow-up time of 3.6 years, 25 patients are alive (15 in group 1, 10 in group 2). The mean overall survival was similar for patients of both groups (49 weeks and 48 weeks, respectively) (Fig. 1). The type of surgical procedure was the most significant prognostic factor ($p = 0.001$): 5-year actuarial survival was 3% after palliative resection (mean survival 39 weeks versus 37 weeks), 21% after curative resection (90 weeks versus 93 weeks) (Fig. 2). In curative resections without lymph node involvement, the mean survival was 76 weeks in group 1 and 111 weeks in group 2, but long-term results were similar (Fig. 3). Considering the local extension of the tumor, the 2 treatment groups were not different in any of the subgroups, except for the 20 patients with mucosal and submucosal growths: mean survival was 142 weeks versus 99 weeks ($p = 0.33$) (Fig. 4). A slight benefit was also observed in upper third lesions: 9 patients in group 1 and 13 in group 2 have had a curative resection; mean survival was 161 weeks and 97 weeks, respectively ($p = 0.04$) (Fig. 5).

The site of progression in resected patients (Table 6) was interesting to consider. While the rate of distant metastases was higher in the combined treatment group, there was a reduction of local recurrences ($p = 0.05$), particularly in curative resections with a lengthening of time to relapse (Fig. 6).
Discussion

The review of the literature shows that fractionated radiation up to 45 Gy is well tolerated and can produce disappearance of the tumor in a small percentage of cases. The low rate of complete responses in 2 randomized trials is probably related to the short interval between the 2 treatments. A period of rest between the radiation and surgery seems associated with a better survival. In prospective studies, however, resection rates are not improved, and radiation therapy has not been demonstrated beneficial on survival (Figs. 1 and 2), except perhaps in a small group of selected patients with localized tumors who respond well to radiotherapy. As pointed out by Ellis et al. [19], tumors in the cervical and upper thoracic region, which are better cured by radiation alone, are also more accessible to the combined approach. Results in lymph node-negative tumors in the E.O.R.T.C. trial contradict the results of postoperative radiation in the report of Kasai. Indeed, there is an intersection of survival curves in the E.O.R.T.C. trial (Fig. 3). Even though the combined treatment may delay the appearance of local recurrence (Fig. 6), this benefit is not translated into a survival benefit. This fact clearly indicates the limits of local therapy in patients with esophageal carcinoma, of whom two-thirds have disseminated disease [3, 4, 20]. To conclude, as emphasized by Kelsen et al. and as shown in the E.O.R.T.C. trial, there is no argument to recommend preoperative radiation as a routine

Table 6. Site of progression in resected patients (postoperative deaths excluded).

<table>
<thead>
<tr>
<th>Group 1 (Combined treatment)</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No progression</td>
<td>15</td>
</tr>
<tr>
<td>Local</td>
<td>12</td>
</tr>
<tr>
<td>Distant</td>
<td>15</td>
</tr>
<tr>
<td>Both local and distant</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
</tr>
</tbody>
</table>

Fig. 3. Survival after curative resection without lymph node invasion.

Fig. 4. Survival after resection for superficial carcinomas.

Fig. 5. Survival after curative resection for upper third lesions.

Fig. 6. Time to local recurrence by treatment group in resected patients.
procedure. This approach could be beneficial to carefully selected patients, but the question is whether identical results could not be obtained by radiation alone in those patients.

Postoperative radiation in patients with resectable disease is most appropriate with regard to the assessment of extension, but presents some disadvantages (lower radiosensitivity of ischemic tissues, presence of the transplant). Radiation is able to eradicate microscopic disease in the neck and mediastinum and to enhance local control [21], but without evident improvement in overall survival. Suggestion of benefit in patients without nodal metastases [20] was not confirmed in the preliminary results from a French randomized trial (A.U.R.C., unpublished data).

Approaches using both local and systemic therapy have been recently reviewed [22]. Combinations of chemotherapy and radiation prior to surgery, with the intent to enhance the effectiveness of radiation and to act against disseminated disease, are limited by the lack of very effective regimens in esophageal cancer, and by the toxicity of these treatments prior to surgery. Although preliminary results are encouraging, these approaches must still be considered experimental.

Résumé

Resumen
Los intentos de combinar radioterapia con cirugía en casos operables de carcinoma de esófago se iniciaron hace 30 años. Las primeras series quirúrgicas reportadas mostraron un bajo índice de resectabilidad y una elevada mortalidad post-operatoria. Los resultados de la radioterapia sola también fueron decepcionantes a largo plazo, especialmente en pacientes que aparecían como de excelente riesgo operatorio con tumores pequeños y localizados. La razón para un enfoque combinado era que la radioterapia podría reducir el tamaño y actividad del tumor, lograr una mejoría del estado nutricional al restablecer la capacidad de deglución, disminuir la "trasplantabilidad" del tumor, y obtener un efecto curativo sobre la enfermedad regional periesofágica que no es susceptible de adecuado tratamiento con la cirugía. Por otro lado, la cirugía con frecuencia permitía una resección ampliada, con lo cual se limpiaban focos residuales o extensión distal en la pared esofágica. El límite del enfoque combinado es la toxicidad de la radiación preoperatoria, la cual debe ser lo suficientemente leve como para permitir realizar la cirugía sin excesiva demora ni incremento en la mortalidad operatoria. Numerosos programas de radioterapia fueron utilizados sobre diferentes campos y con diversas dosis y fraccionamientos, la mayoría en estudios no aleatorizados. Dos estudios prospectivos y aleatorizados han sido informados recientemente. Los resultados finales de un tercer ensayo prospectivo, bajo la EORTC (Organización Europea para la Investigación y el Tratamiento del Cáncer), son presentados.

References