Multiple Management Modalities in Esophageal Cancer: Combined Modality Management Approaches

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ABSTRACT

The overall success rate nationally in treating esophageal carcinomas remains poor, with over 90% of patients succumbing to the disease. In part I of this two-part series, we explored epidemiology, presentation and progression, work-up, and surgical approaches. In part II, we explore the promising suggestions of integrating chemotherapy and radiation therapy into the multimodal management of esophageal cancers.

Alternative approaches to resection alone have been sought because of the overall poor survival rates of esophageal cancer patients, with failures occurring both locally and distantly. Concomitant chemotherapy and radiation therapy (XRT) have been shown, by randomized trial, to be more effective than XRT alone in treating unresectable esophageal cancers and also have shown promise as a neoadjuvant treatment when combined with surgery in the multimodal treatment of this disease. Various studies have also addressed issues such as preoperative chemotherapy, radiation dose escalation, chemotherapy/XRT as a definitive treatment versus use as a surgical adjuvant, and alternative chemotherapy regimens. There are suggestions of some progress, but this remains a difficult problem area in which management is continuing to evolve.

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INTRODUCTION

The long-term outlook for esophageal cancer patients, traditionally treated by surgical approaches, has been bleak. Half the patients are unresectable or metastatic at presentation. Surgery alone may provide good disease-free survival times for very early-stage, superficial cancers, but the
majority of patients have local-regional failure and progression to distant metastases when treated with surgery alone. There has, therefore, been a variety of attempts to use radiation therapy (XRT) or chemotherapy, or both, in the treatment of esophageal cancers.

Preoperative Radiation with Surgery

The intent with preoperative radiation is to improve local control by reducing tumor bulk, sterilizing nodal areas, and reducing the risk of dissemination at surgery. Nakayama et al. first reported retrospective data showing favorable results with the use of preoperative radiation [1]. Subsequently, however, six randomized trials and a meta-analysis have failed to confirm benefit [2-8]. Most of these trials, however, employed suboptimal doses and radiation techniques and did not allow 4-6 weeks between irradiation and surgery [2-8]. Two trials reported survival benefits, but the data are suggestive, not conclusive. Nygaard et al., in a four-arm randomized trial, reported 3-year survival rates of 5% in the control arm and 20% in those patients receiving preoperative radiation [2]. Only patients with squamous cell carcinoma (SCC) were included, and the results did not reach statistical significance. Additionally, there was a greater percentage of patients with early, stage T1 disease in the radiation-only arm, and half the patients received chemotherapy. Huang et al. also reported a superior survival rate (46% versus 25%) in favor of preoperative radiation; however, no statistical analysis was reported [8]. Launois et al. analyzed 67 patients with SCC who received 40 Gy of radiation over 8-12 days and surgery within 8 days and found no difference in resectability or in the 5-year survival rate (9.5% in the XRT arm and 11.5% in the control) [3]. The European Organization for Research and Treatment of Cancer (EORTC) also conducted a trial, evaluating 102 patients with SCC who had preoperative XRT, and noted no difference in overall survival or resectability, but did detect a lower rate of local failure in the radiation arm, 46% versus 67%, which did not reach statistical significance [4]. We conclude that some data are suggestive of better local control, but, at present, preoperative radiotherapy has not been proven to improve the survival of patients with esophageal cancer.

Postoperative Radiation Therapy

The goal of postoperative radiation therapy is to decrease the risk of local recurrence and thereby contribute to a potential survival benefit. In 1976, Kasai et al. first reported that a course of postoperative radiation in patients undergoing surgery with no metastatic lymph nodes resulted in longer survival [9]. However, two randomized trials followed and failed to corroborate those results. Teniere et al. randomized 221 patients with SCC to either 45-55 Gy of radiation (at 1.8 Gy/fraction) postoperatively or surgery alone and found no difference in overall survival, but did observe a lower rate of local recurrence, 10% versus 35%, that was significant only in those patients with negative nodes [10]. Fok et al. randomized 130 patients with SCC or adenocarcinoma (AC) to either palliative or curative surgery alone or surgery followed by 3.5 Gy/fraction of radiation over a 3-week period to 49 Gy for the curative group and to 52.5 Gy for the palliative group. Local recurrence was significantly lower, 20% versus 46%, only in the group undergoing palliative resection; there was no impact on local recurrence in patients who underwent curative resection or on overall survival in all patients [11]. The high dose per fraction used in that study may have contributed to the 37% incidence of gastric complications and the 8% rate of treatment-related fatalities [11]. Postoperative radiation may play a role in decreasing local recurrence in the setting of positive margins, but it has not been shown to change overall survival or have any impact on patients with positive nodes.

Radiation Therapy Alone

Radiation alone, delivered as a definitive modality in the treatment of esophageal cancer, is usually reserved for patients who are unable to receive chemotherapy, as it has clearly been proven in randomized trials to be inferior to chemoradiation. In general, when radiation alone is delivered, median survival is in the range of 6-12 months, and the 5-year survival rate is less than 10% [12, 13]. High local failure rates, ranging from 68%-84%, have been reported in the radiation-only control arms of phase III trials and are the primary reason why radiation alone is rarely curative for this disease [14, 15]. Sykes et al. reported on 101 patients (90% with SCC) with early-stage disease (all tumors <5 cm) treated to 45-52.5 Gy of radiation in 15-16 fractions, observing a 5-year survival rate of 20% [16]. Wan et al., in randomized studies, analyzed dose escalation and accelerated hyperfractionation and found no added survival benefit [17]. Thus, the role of XRT alone as a definitive approach is limited; it should probably be viewed as a palliative approach.

Combined Chemoradiation Therapy

The use of chemoradiation as definitive therapy in the treatment of esophageal cancer has gained rapid acceptance in the community and has been found to be superior to radiation alone in several randomized trials [18, 19]. Prior to randomized trials, several nonrandomized studies reported encouraging results for definitive chemoradiation [20-22]. At the Princess Margaret Hospital (Toronto, Canada), 35 patients with SCC of the esophagus were treated with infusional 5-fluorouracil (5-FU) and mitomycin-C and external beam radiation doses of 40-50 Gy in continuous or split courses. When
compared with historical controls receiving radiation alone, there was a significant advantage in overall and relapse-free survival rates noted for patients receiving single, continuous-course XRT (2-year survival rate of 28% versus 15%, \( p = 0.004 \)) [20]. Other independent studies revealed 2-year survival rates ranging from 28%-55%, which are comparable with results achieved with surgery alone and better than historical results achieved with radiation alone [20-23]. From 1980-1989, Coia et al. prospectively studied 90 patients and separately analyzed those with early-stage disease [22]. Both SCC and AC subtypes were included, and the average follow-up was 45 months; 57 patients with stage I or II disease received 60 Gy of radiation along with continuous infusion 5-FU (weeks 1 and 5) and bolus mitomycin-C (10 mg/m² on day 2). Patients with stage III or IV disease were palliatively treated with the same chemotherapy but received only 50 Gy of radiation. For the early-stage patients, the 5-year actuarial survival rate was 18%, the 5-year actuarial disease-specific survival rate was 30%, the 5-year local relapse-free survival rate was 70%, and the local failure rate was 25%. Multivariate analysis revealed that stage had a significant effect on survival, with stage I and II patients having 3-year survivals rates of 73% and 33%, respectively \(( p = 0.01)\). In the 29 patients developing recurrent disease, only 48% had any component of local failure, in contrast to the 72% that had distant failure as a component of their failure. The local-regional failure rate with radiation therapy alone in historical series has ranged from 67%-84% [13-15, 21]. The improvement in local control with chemoradiation and the shift in failure from local to primarily distant has been evinced in other studies and illustrates the contribution of chemoradiation to radiosensitization and local control [21].

The results of randomized trials of chemoradiation versus radiation alone are shown in Table 1. A Norwegian study of 96 patients with SCC of the esophagus found no improvement in survival for patients receiving two courses of bleomycin/cisplatin before 63 Gy of radiation [23]. Smith et al. published the results of the Eastern Cooperative Oncology Group (ECOG)/EST-1282 study in which 119 patients were randomized to either concomitant 5-FU/mitomycin-C and 60 Gy of radiation or 60 Gy of radiation alone [25]. The median survival time was significantly longer, 14.9 versus 9.3 months, in the combined modality group. Although there was a nonrandomized option for surgery after 40 Gy of radiation (54 patients proceeded to surgery), analysis of patients receiving surgical resection failed to reveal a survival benefit, compared with patients who did not have surgery. As in the Fox Chase Cancer Center (Philadelphia, PA) study [22], there was a significant correlation between disease stage and survival (median survival of stage I disease was 14.8 months versus only 9.4 months for stage II disease) [25]. The impact of combined modality therapy was found to have a more pronounced effect on survival for patients with primaries in the upper two-thirds of the esophagus, in contrast to those with distal third tumors. The EORTC conducted a trial with 221 patients, randomizing them either to 40 Gy of radiation alone (given as 20 Gy over 5 days \( \times \) 2, split course with a gap of 2 weeks) or the same radiation regimen given with cisplatin (given for four cycles after radiation and before each XRT course). This study detected a significant difference in progression-free survival \((11.3 \text{ versus } 6.2 \text{ months}, p = 0.015)\), longer median survival, and better local control in the group receiving cisplatin; however, overall survival was not affected [26]. Araujo et al. randomized 59 patients with stage II esophageal SCC to either radiation alone (50 Gy in 25 fractions) or chemoradiation with 5-FU on days 1-3, mitomycin-C on day 1 of radiation, and weekly bleomycin [15]. The overall survival rates at 5 years were 16% versus 6% in favor of the combined-modality arm; however, these values did not reach statistical significance \((p = 0.16)\). Patients received only one cycle of 5-FU and mitomycin-C, and the study was underpowered to detect a statistical difference. The Radiation Therapy Oncology Group (RTOG) 8501 trial was the landmark trial that established the superiority of chemoradiation over radiation alone. Herskovic et al., in an Intergroup trial, analyzed 123 patients who were randomized to receive either chemoradiotherapy with 50 Gy of radiation and concurrent adjuvant cisplatin/5-FU or 64 Gy of radiation without chemotherapy [14]. Most patients had SCC and received four cycles of 5-FU \((1,000 \text{ mg/m}^2/24 \text{ hours} \times 4 \text{ days})\) and cisplatin \((75 \text{ mg/m}^2/\text{on day 1})\). Radiation was delivered at 2 Gy/fraction for a total dose of 50 Gy starting on day 1 of chemotherapy, and chemotherapy was subsequently given at weeks 5, 8, and 11. Patients in the control arm received a radiation dose of 64 Gy alone. The median survival time of the combined modality arm was 14.1 months and the 5-year survival rate was 27%; in the control arm, the median survival rate was 9.3 months and no patients were alive at 5 years \((p < 0.0001)\) [27]. In addition, lower rates of local recurrence and distant metastasis were observed in the combined-modality group. Long-term follow-up of those patients, as well as analysis of 69 additional patients who were treated with the same chemoradiation regimen in a nonrandomized fashion, corroborates the original findings of the Intergroup trial [27, 28]. In a 1997 progress report of the RTOG 85-01 trial, al-Sarraf et al. reported a higher rate of both grade III \((44\% \text{ versus } 25\%)\) and grade IV \((20\% \text{ versus } 3\%)\) acute toxicities [27]. Cooper et al., in a 1999 update, observed an 8-year survival rate of 22% in the combined-modality arm and the persistence of higher grade IV toxicity rates \((8\% \text{ versus } 2\%)\), compared with those seen in the
radiation-alone arm [28]. In an attempt to improve on the 44% local control rate achieved in the combined-modality arm of the RTOG 8501 trial, the Intergroup developed a phase II trial (INT 0122) that increased the radiation dose from 50 Gy to 64.8 Gy and intensified the chemotherapy dose from 4 to 5 days per cycle and from a total of four to five cycles with three cycles delivered neoadjuvantly [29]. There was a 39% local recurrence rate and a 9% treatment mortality incidence, which was associated with the neoadjuvant chemotherapy. It was suggested, from this trial, that a dose of 64.8 Gy could perhaps be tolerated. The Intergroup then initiated the INT 0123 trial in which all patients received the same chemotherapy regimen as in the RTOG 8501 trial and were randomized to receive either 50.4 Gy or 64.8 Gy of radiation. Results from that trial failed to show a benefit for local control or survival in the dose-escalated arm [30].

### NEOADJUVANT CHEMOTHERAPY WITH SURGERY VERSUS SURGERY ALONE

Interest in induction chemotherapy followed by esophagectomy originated almost three decades ago when several phase II studies were reported. The presumed advantages of this approach are the downstaging of tumor and clearing of micrometastasis in regional lymph nodes and distant organs.

### Table 1. Randomized trials of chemoradiation (CRT) versus radiation alone

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients</th>
<th>Histology</th>
<th>Radiation dose (Gy/fraction)</th>
<th>Weeks</th>
<th>Gap (weeks)</th>
<th>Chemotherapy agent</th>
<th>Survival at first site (%)</th>
<th>Local recurrence at first site (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Kolaric et al. [107]</td>
<td>51</td>
<td>CRT</td>
<td>40-50</td>
<td>4</td>
<td>5</td>
<td>bleomycin</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>XRT</td>
<td>60-70</td>
<td>4</td>
<td>5</td>
<td>none</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Roussel et al. [108]</td>
<td>170</td>
<td>CRT</td>
<td>56/25</td>
<td>5</td>
<td>5</td>
<td>methotrexate</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>77</td>
<td>XRT</td>
<td>56/25</td>
<td>5</td>
<td>5</td>
<td>none</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Hatlevoll et al. [24]</td>
<td>96</td>
<td>CRT</td>
<td>63/36</td>
<td>9</td>
<td>3</td>
<td>cisplatin/bleomycin</td>
<td>5.5</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>XRT</td>
<td></td>
<td></td>
<td></td>
<td>none</td>
<td>5.5</td>
<td>29</td>
</tr>
<tr>
<td>Araujo et al. [15]</td>
<td>59</td>
<td>CRT</td>
<td>50/25</td>
<td>5</td>
<td>5</td>
<td>5-FU + MMC</td>
<td>15</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>XRT</td>
<td>50/25</td>
<td>5</td>
<td>5</td>
<td>none</td>
<td>15</td>
<td>55</td>
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<tr>
<td>Herskovic et al. [14]</td>
<td>123</td>
<td>CRT</td>
<td>50/25</td>
<td>5</td>
<td>5</td>
<td>cisplatin</td>
<td>14.1</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>61</td>
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<td></td>
<td></td>
<td></td>
<td>none</td>
<td>9.3</td>
<td>34</td>
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<tr>
<td>Slabber et al. [26]</td>
<td>70</td>
<td>CRT</td>
<td>40/10</td>
<td>4</td>
<td>2</td>
<td>5-FU + cisplatin</td>
<td>1.72</td>
<td>63</td>
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<tr>
<td></td>
<td>34</td>
<td>XRT</td>
<td></td>
<td></td>
<td></td>
<td>none</td>
<td>9.2</td>
<td>33</td>
</tr>
<tr>
<td>Smith et al. [25]</td>
<td>119</td>
<td>CRT</td>
<td>40/20</td>
<td>4-6</td>
<td>5</td>
<td>5-FU/MMC</td>
<td>14.8</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>XRT</td>
<td></td>
<td></td>
<td></td>
<td>none</td>
<td>9.2</td>
<td>33</td>
</tr>
<tr>
<td>Earle et al. [110]</td>
<td>77</td>
<td>CRT</td>
<td>50-60</td>
<td>5-6</td>
<td>5</td>
<td>bleomycin</td>
<td>6.2</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>XRT</td>
<td></td>
<td></td>
<td></td>
<td>none</td>
<td>6.4</td>
<td>30</td>
</tr>
</tbody>
</table>

**Abbreviation:** MMC = mitomycin-C

*4-year survival

†nonrandomized
The most commonly used agents are cisplatin and fluorouracil, although some investigators incorporated vinca alkaloids or taxanes into their regimens. Clinical response rates of 40%-65%, pathological complete responses rates of 0%-10%, and resectability rates of 40%-80% were documented in some trials [31-42]. Median survival of these patients was reported to be 18-28 months [31-43]. This treatment regimen can potentially delay definitive surgical resection, although most series did not report such data. The initial concern of increased postoperative morbidity and mortality was not substantiated by subsequent trials [44].

After reports of promising data from nonrandomized trials, several centers conducted phase III randomized trials to test the benefit of preoperative chemotherapy for resectable esophageal carcinoma. There are at least 12 randomized trials reported in the literature [2, 45-55]. Selected trials allowed the use of radiotherapy in combination with chemotherapy. In a randomized trial from the M.D. Anderson Cancer Center, Roth et al. compared cisplatin, vindesine, and bleomycin given pre- and postoperatively with surgery alone and found no significant difference in postoperative morbidity [47]. They reported a 47% response rate in the chemotherapy arm but no improvement in tumor resectability. With a median follow-up of 30 months, patients with good responses to chemotherapy experienced a significant longer overall survival (median survival of 20 months) compared with nonresponders (6.2 months) or with those receiving surgery alone (8.6 months).

On the other hand, the North American Intergroup trial by Kelsen and colleagues, which also tested the value of preoperative chemotherapy in a multi-institutional randomized setting, did not show any benefit of preoperative chemotherapy over surgery alone [51]. One criticism of that study was that only 70% of patients received all planned chemotherapy cycles, but the chemotherapy regimen itself was more intense: three cycles of cisplatin/fluorouracil were prescribed preoperatively, and an additional two cycles were given after surgery. Eighty-four percent of patients received at least two cycles of chemotherapy before surgery. Survival analysis revealed a 14.9-month median survival in the chemotherapy arm compared with 16.1 months for the immediate surgery group ($p = 0.52$).

Recently, a randomized study from the United Kingdom conducted by the Medical Research Council was published in the journal *Lancet* [56]. In that trial, preoperative chemotherapy consisted of two cycles of cisplatin and 5-FU with a slightly higher dose of cisplatin (80 mg/m$^2$). Better adherence to chemotherapy was achieved, with 90% of patients receiving both cycles of chemotherapy. Clinicians were allowed to give radiation therapy at their discretion, but only a few patients received it. That study reported slightly higher resectability rates (60% versus 54% $p < 0.001$), with a statistically significant benefit in overall survival for patients who received neoadjuvant chemotherapy: 2-year survival rates of 43% versus 34%.

Most studies that have tested the benefit of preoperative chemotherapy reported acceptable toxicities, and postoperative morbidity was not significantly greater from adding chemotherapy before surgical resection; however, there has been no significant improvement in resectability rates. The two major randomized trials, the Intergroup trial published by Kelsen et al. [51] and the British Medical Research Council study [56], arrived at opposite conclusions; the former found no real benefit to adjuvant chemotherapy, while the latter did report a modest benefit in survival. This has given little impetus to the use of chemotherapy alone in the neoadjuvant or adjuvant setting.

**NEOADJUVANT CHEMORADIOThERAPY**

Radiation therapy has an integral role in the management of esophageal carcinoma, and many investigators have tested its potential benefit in the preoperative setting. Although preoperative radiation alone showed no benefit in disease outcome, multiple studies demonstrated a clear advantage in using combined chemoradiation in the neoadjuvant setting.

Several nonrandomized trials from different institutions have reported good response rates from neoadjuvant chemoradiation [57-70]. Jones and colleagues from the University of North Carolina at Chapel Hill (Chapel Hill, NC) showed minimal toxicities from 45 Gy of radiation therapy combined with 5-FU and cisplatin chemotherapy given prior to surgery. The 36-month survival rate for patients who achieved pathologic complete responses (41% of the group) was not significantly different from that of nonpathologic complete response patients (45% versus 23%, $p = 0.13$), but the difference in relapse-free survival was significant ($p = 0.007$) [61].

A pilot study from Wayne State University (Detroit, MI) by Leichman et al. selected patients with squamous cell histology for preoperative chemoradiotherapy with 5-FU and cisplatin combined with 30 Gy of radiation over 3 weeks. Of the 71% of patients who underwent curative resection, pathologic complete responses in the primary tumor site were detected in 47%, and a 27% operative mortality rate was observed. The median survival time for good responders was 24 months, and median survival time was 18 months for all patients enrolled in the study [62]. The Southwest Oncology Group (SWOG) 8037 trial, which evaluated 113 patients, used a similar regimen of concurrent 5-FU and cisplatin and 30 Gy of radiation before surgery. After preoperative treatment, only 71 patients underwent surgical resection, with an operative mortality rate of 11%; the 3-year actuarial survival rate was 16% but none of the patients were alive at 4 years [63].
Several series have been published from the University of Michigan on preoperative chemoradiotherapy for resectable esophageal carcinoma. That institution used transhiatal resection as a surgical technique. In a series from Forastiere and colleagues, which included both AC and SCC, patients received preoperative radiotherapy with 44 Gy in 22 fractions combined with cisplatin/5-FU. Ninety percent of patients had tumor resection with negative margins and 40% had complete pathologic responses. Median survival for all patients in that group was 31.3 months, with a 2-year survival rate of 58%, compared with a 58-month median survival and a 78% 2-year survival rate for patients with complete tumor responses after induction chemoradiotherapy [71].

There has been an attempt to optimize preoperative chemoradiotherapy with various approaches; one of these is intensification of the radiotherapy regimen with hyperfractionation [72-76]. Some studies reported higher complete response rates at the expense of greater acute toxicities [73], but others did not detect much improvement in outcome [61, 71, 75, 77]. In addition, the use of brachytherapy to intensify the radiation dose has resulted in significant toxicity, as evinced by the results of a single, large, randomized trial evaluating the role of brachytherapy (RTOG 92-07) [78].

Do patients who achieve complete responses still need aggressive surgical treatment? Some studies reported lower local failure rates in patients who underwent surgical resection than in those who received chemoradiotherapy only, with no difference in survival [79], although a Patterns of Care survey study [80] reported a significant improvement in survival for patients selected to receive preoperative combined-modality therapy compared with chemoradiotherapy alone.

There have been three randomized trials comparing preoperative combined-modality therapy with surgery alone in patients with clinically resectable disease [81-85]. Urba and associates, from the University of Michigan [82, 83], randomized 100 patients to receive either preoperative cisplatin (20 mg/m² on days 1-5 and 17-21), vinblastine (1 mg/m² on days 1-4 and 17-20), 5-FU (300 mg/m²/24 hours on days 1-21), and concurrent radiation therapy (1.5 Gy twice a day to 45 Gy) followed by a transhiatal esophagectomy or surgery alone. Their preliminary analysis showed no benefit in median survival (1.46 versus 1.48 years) or the estimated 2-year survival rate (41% versus 36%) of preoperative combined-modality therapy. Subsequent analysis with a longer follow-up (median 5.2 years) revealed no improvement in median survival (1.41 versus 1.46 years); a significantly lower local recurrence rate (19% versus 39%; \( p = 0.04 \)) was observed in patients who received combined-modality therapy. A 3-year survival advantage was a borderline statistically significant finding in the preoperative chemoradiotherapy group (32% versus 15%; \( p = 0.07 \)) by univariate analysis and reached statistical significance with multivariate analysis (\( p = 0.04 \)). Walsh et al. [84] reported a randomized trial of 113 patients with AC of the midesophagus or distal esophagus (including the cardia). Their preoperative treatment included two cycles of 5-FU (15 mg/m²/24 hours on days 1-5) and cisplatin (75 mg/m² on day 7) and concurrent preoperative radiation therapy (2.67 Gy/day to 40 Gy). With a median follow-up in surviving patients of 8 months, a significantly higher median survival time (16 versus 11 months, \( p = 0.01 \)) and 3-year survival rate (32% versus 6%; \( p = 0.01 \)) were observed in patients who received preoperative therapy compared with those treated with surgery alone. A major criticism of that trial is the high operative mortality (9%) and the low 3-year survival rate (6%) in the surgical control arm. Bosset et al. reported the results of a third randomized trial of preoperative combined-modality therapy from the EORTC [85]. A total of 282 patients with clinically resectable SCC was randomized to receive either preoperative combined-modality therapy or surgery alone. The combined-modality therapy regimen was unconventional in design, with higher radiation doses per fraction (3.7 Gy) and a split course with a 2-week rest. The chemotherapy regimen was also inadequate, with cisplatin given at a dose of 80 mg/m² on days 0-2 before starting radiation therapy. The 3-year disease-free survival rates were 40% versus 28% favoring the preoperative combined-modality group, but there was no improvement in median survival (19 months) or the overall 3-year survival rate (36%) compared with patients treated with surgery alone. Results of these three randomized trials should be interpreted with caution because of the low numbers of patients, short follow-up, and limitations in the treatment details.

In summary, there is a clear trend toward superior outcomes for patients who receive preoperative chemoradiotherapy, without much toxicity. Because of heterogeneity in patient selection and treatment regimens, it is difficult to interpret the outcome data. Hopefully, new studies that use a treatment approach with optimal chemotherapy and radiotherapy regimens will solidify multimodality treatment.

**NEW EMERGING THERAPIES**

The treatment strategy of preoperative chemotherapy and radiation followed by surgery is gaining momentum because single-institution trials suggest superior local control and survival rates. However, it has been difficult to prove that this approach is superior to surgery alone in randomized group trials. The U.S. Intergroup trial, Cancer and Leukemia Group B C9781, attempted to answer this question...
by employing 5-FU, cisplatin, and radiation prior to surgery against surgery alone; unfortunately the trial was terminated as a result of poor accrual. A contributing factor to the poor accrual may have been the lack of consensus about an optimal regimen of preoperative chemoradiotherapy, especially with the shift to an increasing incidence of adenocarcinomas.

The identification of new active agents for esophageal cancers, such as the taxanes and irinotecan, provides an opportunity to improve outcome of preoperative chemoradiotherapy in phase II studies prior to further cooperative group randomized trials.

Based on multiple trials, the most effective single chemotherapeutic agent established for treating esophageal cancer in the adjuvant or metastatic setting is cisplatin [86-90]. Fluorouracil has synergistic activity with cisplatin and also acts as a radiosensitizer; more recently, it has largely replaced other agents, such as bleomycin and mitoguazone. Paclitaxel-based chemotherapy regimens have been tested for esophageal carcinoma with some promising results [57, 58, 91, 92]; however, a higher rate of acute radiation esophagitis has been seen in initial reports [58]. Initial studies that employed a 24-hour infusion regimen revealed unacceptably high toxicities [93]. More protracted infusions appear to be better tolerated [94]. Strategies to combine paclitaxel with cisplatin, with or without 5-FU, are being investigated. Paclitaxel, a synthetic microtubule inhibitor, appears to be a radioenhancing agent, possibly synchronizing cells in the radiosensitive G₂/M portion of the cell cycle. Paclitaxel alone, or with cisplatin, has demonstrated a high response rate in recurrent or metastatic esophageal cancer with response rates of 40% (15% complete response) with paclitaxel given at a dose of 250 mg/m² every 21 days and cisplatin at a dose of 50 mg/m² repeated every 14 days [95, 96]. In locally advanced esophageal carcinoma, a 47% response rate was seen with paclitaxel at a dose of 200 mg/m² over 24 hours and cisplatin at a dose of 75 mg/m² given twice [97]. In a phase I study from the Fox Chase Cancer Center, 29 patients

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients</th>
<th>Sequence</th>
<th>Chemotherapy</th>
<th>Radiation dose</th>
<th>Response rate</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coia et al. [22]</td>
<td>90</td>
<td>definitive</td>
<td>5-FU, Mitomycin-C</td>
<td>60 Gy, 1.8 Gy/fraction</td>
<td>–</td>
<td>18% at 5 years</td>
</tr>
<tr>
<td>Jones et al. [61]</td>
<td>166</td>
<td>definitive</td>
<td>cisplatin, 5-FU</td>
<td>45 Gy, 1.8 Gy/fraction</td>
<td>41%</td>
<td>45% at 3 years</td>
</tr>
<tr>
<td>Leichman et al. [62]</td>
<td>21</td>
<td>neoadjuvant</td>
<td>cisplatin, 5-FU</td>
<td>30 Gy, 2 Gy/fraction</td>
<td>47%</td>
<td>18 months</td>
</tr>
<tr>
<td>Poplin et al. [63]</td>
<td>71/113</td>
<td>neoadjuvant</td>
<td>cisplatin, 5-FU</td>
<td>30 Gy, 2 Gy/fraction</td>
<td>25%</td>
<td>12 months</td>
</tr>
<tr>
<td>Forastiere et al. [71]</td>
<td>45</td>
<td>neoadjuvant</td>
<td>cisplatin, 5-FU</td>
<td>44 Gy, 2 Gy/fraction</td>
<td>40%</td>
<td>32 months</td>
</tr>
<tr>
<td>Bains et al. [99]</td>
<td>36/41</td>
<td>neoadjuvant</td>
<td>cisplatin, paclitaxel</td>
<td>50.4 Gy, 1.8 Gy/fraction</td>
<td>22%</td>
<td>–</td>
</tr>
</tbody>
</table>
with resectable carcinoma were treated with 60 Gy of radiation (2 Gy daily for 6 weeks) and concurrent chemotherapy: a continuous infusion of 5-FU (200-225 mg/m²/day), paclitaxel (25, 40, 50, or 60 mg/m²) weekly over 1 hour, and cisplatin (25 mg/m²) weekly immediately following paclitaxel throughout radiation. Patients received either four cycles of postoperative paclitaxel (175 mg/m² over 3 hours) and cisplatin (75 mg/m² every 3 weeks) or paclitaxel (175 mg/m² over 3 hours) and cisplatin (75 mg/m² every 3 weeks) prior to the initiation of chemoradiation. After induction therapy and restaging, esophagectomy was performed 4-6 weeks later. Twenty-seven patients were eligible for study. The maximum tolerated dose combination was paclitaxel at 50 mg/m² over 1 hour weekly, cisplatin at 25 mg/m² over 1 hour weekly, 5-FU at 200 mg/m²/day by continuous infusion throughout radiotherapy, and radiation to 60 Gy. Twenty-two patients completed therapy and underwent surgical resection; four patients had complete pathological responses and 18 had partial responses with no mortality. The most common dose-limiting toxicities were mucositis and esophagitis. The median follow-up time of 22 patients undergoing esophagectomy was 205 weeks (range 26-303 weeks). At 4 years follow-up, 10 of 22 patients (45%) were alive and free of disease [98].

Bains and colleagues at the Memorial Sloan Kettering Cancer Center conducted a phase II trial of neoadjuvant cisplatin (75 mg/m²) and paclitaxel (175 mg/m²) for two cycles followed by combined cisplatin (30 mg/m² weekly), paclitaxel (30-80 mg/m²), and radiation therapy (50.4 Gy) prior to surgery. Forty-one patients were enrolled, and 36 patients completed treatment. The symptoms of dysphagia improved in 35 of 38 (92%) patients after induction chemotherapy. Thirty-five percent of patients who underwent induction chemotherapy and 10% who underwent chemoradiation experienced grade III/IV myelosuppression. Nine of 36 patients (22%) achieved pathological complete responses and 33 of 36 patients (92%) underwent resections with no residual tumor at operation. Only two patients (5%) experienced grade III esophagitis. This regimen was well tolerated, produced rapid dysphagia relief, and was associated with a high resection and pathological complete response rate. It should be further evaluated in phase III trials [99]. Three trials using interferon-alpha(2a) as a biomodulator of 5-FU suggested possible benefit [100, 101]. Ilson et al. [102] reported 50% complete and partial response rates in patients with metastatic disease treated with a combination of interferon, cisplatin, and 5-FU. Interferon in combination seems to have more benefit for SCC rather than AC patients.

Irinotecan in combination with cisplatin has significant activity in metastatic esophageal cancer and relieves dysphagia [103-104]. In vitro studies have demonstrated synergy for these drugs, and two trials have yielded encouraging results [104, 105]. Irinotecan, a semisynthetic derivative of camptothecin, is a topoisomerase-I inhibitor and appears to be a radioenhancing agent, possibly by inhibiting the repair of potentially lethal radiation injury to DNA as well as cell cycle effects. Data demonstrate that platinum and irinotecan can be given safely with thoracic radiotherapy, and this regimen is being investigated in esophageal cancer. Anderson et al. from Memorial Sloan Kettering Cancer Center are conducting a phase I trial of cisplatin plus an escalating dose of irinotecan weekly with concurrent radiation in locally advanced esophageal cancer. Induction chemotherapy with cisplatin at a dose of 30 mg/m² and irinotecan at a dose of 65 mg/m² is given for one cycle, followed by 6 weeks of radiation therapy (50.4 Gy, 1.8 Gy/fraction), with the cisplatin dose fixed at 30 mg/m² and the irinotecan dose escalated in cohorts of three patients (40, 50, 65, 80, 110 mg/m²). Both drugs are given on days 1, 8, 22, and 29 with concurrent radiation. Surgery is performed after chemoradiation. Twelve patients were entered and nine patients completed the first three-dose level (65 mg/m² highest). Six of nine patients had improvement in their dysphagia and six patients underwent surgical resection. Two of six patients had pathological complete responses and four patients were downstaged. No patients developed esophagitis or nonhematological toxicities greater than grade 1/2 except for one patient with reversible pneumonitis at the 50-mg/m² dose level. This regimen has antitumor activity, and further dose escalation of irinotecan is planned [106].

Although single-institution studies give us suggestions of potent new regimens, Intergroup randomized trials more clearly prove the effectiveness of new regimens in a mix of academic and private institutions. To test the efficacy of the paclitaxel/cisplatin or paclitaxel/irinotecan combinations preoperative with radiation, the ECOG is conducting a phase II trial (ECOG 1201) of these agents. In arm 1 of that study, patients receive cisplatin (30 mg/m²) followed by irinotecan (65 mg/m²) on days 1, 8, 22, and 29 of preoperative radiation to 45 Gy followed by surgical resection; after 4 weeks, adjuvant cisplatin (30 mg/m²) followed by irinotecan (65 mg/m²) is given on days 1 and 8 for three cycles. Arm 2 employs paclitaxel (50 mg/m²) followed by cisplatin (30 mg/m²) on days 1, 8, 15, 22, and 29 followed by preoperative radiation to 45 Gy followed by surgical resection; after 4 weeks, adjuvant chemotherapy is given with paclitaxel at a dose of 175 mg/m² followed by cisplatin at a dose of 75 mg/m² on days 1 and 3 for three cycles. This trial will test the overall complete response rates between these two treatment strategies as well as toxicity and survival. The best regimen will be compared with the standard cisplatin/5-FU/radiation-based therapy in a randomized trial. Patients that are candidates for preoperative chemoradiation before surgery should be considered for ECOG 1201.
Another emerging drug with activity against esophageal cancer is oxaliplatin. Oxaliplatin (trans-1,2-diaminocyclohexane oxalato-platinum [OXP]) is a novel antineoplastic platinum analogue with a potentially more favorable toxicity profile than cisplatin. At clinically effective doses, OXP is less emetogenic, less nephrotoxic, and less neurotoxic than cisplatin. Similarly, at these doses, it has considerably less bone marrow toxicity than carboplatin. Although 5% of patients experience dose-limiting neurotoxicity with cumulative OXP doses approaching 750 mg/m², this toxicity is more readily reversed than that reported with cisplatin. Of great interest, but through unknown mechanisms, OXP seems to confer renewed sensitivity to approximately 25% of human colorectal tumors previously resistant to 5-FU. In an attempt to assess the activity of OXP in combination with protracted infusion (PI) 5-FU, Khushalani et al. at Roswell Park Cancer Institute (Buffalo, NY) conducted a phase I dose-escalation trial to determine the maximum tolerable dose of OXP that could be safely given with PI 5-FU and radiation in patients with stage II, III, and IV esophageal cancer [111]. The treatment plan for cycle 1 consisted of OXP (85 mg/m²) on days 1, 15, and 29, PI 5-FU (180 mg/m²/24 hours) for 35 days, and XRT of 1.8 Gy/fraction in 28 fractions starting on day 8. At completion of cycle 1, eligible patients could undergo surgery or begin cycle 2 without XRT. Postoperative patients were eligible for cycle 2. Stage IV patients were allowed three cycles in the absence of disease progression. OXP and 5-FU increases were based on dose-limiting toxicity encountered in cohorts of three consecutive patients.

**Conclusion**

The management of esophageal cancer has evolved from surgery alone to definitive chemoradiation and preoperative chemoradiation. A variety of different approaches is available as treatment modalities for this disease, and stage-directed therapy may prove useful. Surgery remains the standard to which all other modalities are compared and is an acceptable option for patients with early-stage disease. For patients with locally advanced disease who are not surgical candidates, definitive chemoradiation with concurrent and adjuvant cisplatin/5-FU has been established as the present standard of care. One troublesome point relates to the extent of radiation fields; the Japanese surgical data suggest that cervical lymph nodes are involved more frequently than we may have appreciated [112]. This suggests extension of radiation fields to cover the neck, but this would be expected also to increase treatment toxicity. There are no randomized data to clearly support dose escalation beyond 50.4 Gy when employing definitive chemoradiation. However, while chemoradiation results in a lower local-regional failure rate relative to XRT alone, Herskovic et al. still reported a 44% local-regional failure rate with the combined-modality treatment [14], which leads to the implication that 50 Gy is an inadequate dose for control. Definitive chemoradiation has resulted in overall survival and local control rates that are comparable with those achieved with surgery alone and has been proven to be superior to radiation alone. Local failure continues to be a significant and troubling component of this disease. Preoperative chemoradiation has been shown to benefit local control and progression-free survival and holds promise as the direction for the future. Novel chemotherapeutic agents, including paclitaxel, irinotecan, and oxaliplatin, may play roles in the reduction of distant metastases. We have some early phase I and II studies with promising results, but data must be more mature to recommend any of these novel agents for treatment of localized or metastatic esophageal carcinoma outside the confines of a clinical trial. Randomized trials employing preoperative chemoradiation, particularly with new chemotherapeutic agents, should be supported so that we may continue to make advances with this disease.

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