Combined-modality therapy in the treatment of local-regional esophageal cancer

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Introduction

Esophageal carcinoma is a lethal disease which carries an ominous prognosis. While survival rates have not changed substantially in recent years, the epidemiology of the disease is undergoing dramatic and as yet poorly understood changes. Esophageal carcinoma continues to be a common disease in many sections of the world, including much of Asia, the Middle East, and South Africa; it is less so in the United States and Western Europe, although areas of high incidence do exist in these regions.

Historically, the vast majority of esophageal cancers have been of the epidermoid or squamous cell type. In the United States, alcohol abuse, tobacco abuse, and lower socioeconomic status are relative risk factors for this type of esophageal cancer. Although the incidence of epidermoid cancer of the esophagus has remained relatively stable, the incidences of adenocarcinomas of the esophagus, gastroesophageal junction, and gastric cardia have risen dramatically over the past two decades [1], and this trend appears to be continuing; adenocarcinomas of the esophagus and proximal stomach are now increasing at a rate which exceeds that of any other cancer in the United States. These cancers are occurring mostly in white males, and appear not to be associated with the same risk factors typically associated with epidermoid carcinomas. A similar trend has been noted by investigators in Great Britain [2]. Thus, esophageal cancer, already a significant public health problem in much of the world, is becoming an issue of increasing proportions in Western countries as well.

Due to the relative scarcity of cases of adenocarcinoma of the esophagus until recently, fewer clinical trials limited to this histologic subtype have been conducted to date. However, the majority of available data do not indicate substantial differences in response to therapy or in survival between epidermoid and adenocarcinomas of the esophagus. Survival data from two surgical series do not show a difference in outcome between the two histologies [3, 4]. In a combined-modality trial involving 90 patients, the survival curves for patients with squamous cell and adenocarcinomas were virtually identical [5]. Thus, at present, our treatment and research strategies for the two histologic subtypes of esophageal cancer are essentially the same. However, it would seem prudent in current clinical trials to stratify patients on the basis of histology, so that any differences that may exist might be noted in the future.

The standard approaches for management of local-regional esophageal cancer have been surgery or radiation therapy. While surgeons point out that esophagectomy provides rapid and effective palliation of dysphagia, radiation therapists note that treatment with radiation avoids the risks of surgical morbidity and mortality. Although a randomized trial comparing surgery alone to radiation therapy alone has not been, and in all likelihood will never be done, all would agree that the results of either surgical management or radiation therapy in terms of disease-free and overall survival are dismal, with 5 year survival rates usually in the 0%-10% range with radiotherapy [6] and 10%-20% with surgery [3, 4, 7]. It should be noted that patients undergoing surgery are usually highly selected, patients with significant co-morbid disease often being excluded.

Because of these poor results, investigators have endeavoured to combine multiple treatment modalities in order to improve patient survival. These combination strategies, their rationales, and their reported results thus far, will be reviewed below.

Preoperative radiotherapy

The earliest reported attempts at combined-modality therapy for esophageal cancers involved the use of preoperative radiotherapy followed by surgery. There are several rationales for this approach. The primary
goal is to reduce tumor bulk and thereby increase the resectability rate, and hopefully improve local control and long term survival rates as a result. Some authors have speculated that those cancer cells most likely to be disseminated through surgery are in areas with rich vascular supply; these cells will therefore be well oxygenated, thus making them more sensitive to radiotherapy. Preoperative radiotherapy might therefore reduce the risk of iatrogenic dissemination of tumor [8]. A further rationale is that the potentially improved nutritional status as a result of response to radiation may decrease surgical morbidity and mortality rates.

Most reports of preoperative radiation therapy have consisted of single arm trials, often reported against historical controls [9–13]. In the five above-referenced studies, a total of 673 patients were entered, with resection being performed in only 254 (38%) [14]. The percentage of patients in each study who were resectable ranged from 30% to 55%. Two Japanese studies reported resection rates of 82% and 73%. Overall treatment mortality rates ranged from 12% to 30%. Owing to the lack of appropriate controls, and to the absence of survival data in many of the reports, no judgements as to the benefits, or lack thereof, of preoperative radiotherapy can be drawn from these studies.

However, several trials have now evaluated preoperative radiotherapy in a prospective, randomized fashion. The first such study randomized 124 patients to receive either 4000 cGy followed by esophagectomy within 8 days of completion of radiotherapy, or esophagectomy alone [15]. Radiotherapy was administered on a somewhat unorthodox schedule over 8 to 12 days. The resection rates and operative mortality rates were high in both treatment groups, however these parameters were comparable in both arms (resection rates and operative mortalities of 70% and 21% for operation alone and 76% and 23% for radiation plus operation). Median survivals for the combined-modality arm and control arm were 4.5 and 8.2 months respectively, and 5 year survival rates, which were reported without inclusion of surgical mortality, were 9.5 and 11.5 percent, respectively (differences not statistically significant).

A subsequent trial conducted by the EORTC utilized a lower preoperative radiotherapy dose [14]. Again, the radiotherapy schedule was somewhat unorthodox, with 3300 cGy given in 10 fractions. Two hundred twenty-nine patients were randomized, and 208 were fully evaluable. Of the evaluable patients, 199 were male. Treatment groups were well matched for tumor stage and location. Resectability rates for the combined-modality and control groups respectively were 81% and 75%, although curative resection was reported in only 56% of patients in each arm, the others undergoing what was classified by the surgeon as a palliative resection. Operative mortalities were 24% and 19% in the combined modality and control groups, respectively. Preoperative radiotherapy did not effect the incidence of lymph node metastases in resected specimens, which were 56% and 58% in the two groups. The mean overall survivals in the two groups were 48 and 49 weeks, with 5 year survival rates of 9 and 10 percent.

Finally, a third trial was reported from the Chinese Academy of Medicine in Beijing [16]. In this trial, 360 patients with squamous cell carcinoma of the midthoracic esophagus were prospectively randomized to receive 4000 cGy, divided into 20 fractions over four weeks, followed by surgery, or surgery alone. High resectability rates and low postoperative mortalities were noted in both treatment arms (90% and 83% resectability, and 3% and 4% postoperative mortality in the combined-modality and surgery-only arms, respectively). The incidence of lymph node metastases was lower in surgical specimens from the patients receiving preoperative radiation (26% versus 39%). Clearly a large percentage of patients in this trial had relatively early stage disease, as 61% of those patients treated by surgery alone had negative lymph nodes at the time of resection. This may help to explain the relatively high survival rates of 47% and 42% at 3 years and 37% and 33% at 5 years in the combined-modality and surgery-only groups, respectively (differences not statistically significant).

In summary, the randomized trials conducted thus far indicate that while there does not appear to be an increase in operative or postoperative complications as a result of preoperative radiation, neither does there appear to be a significant survival advantage. Thus, preoperative radiation therapy cannot be considered to be standard treatment at this time, and its use should be restricted to clinical investigation.

Postoperative radiation

The practice of administering radiotherapy following surgical resection has not been studied in a prospective or systematic fashion. The rationale given for such treatments has been to eradicate either gross disease left behind as a result of positive surgical margins, or to eradicate suspected microscopic residual disease. The former situation would appear to be reasonable under specific circumstances, such as when regional lymph nodes are negative and the positive margin has been well delineated by the surgeon with clips which will be visible during imaging studies for treatment planning. Treatment with postoperative radiotherapy following a complete resection with clean, albeit possibly close margins, is more problematic. There are no good data to support the use of this attempt to ‘sterilize’ the local surgical field. Without the esophagus to serve as a guide, it is difficult to accurately define the lymphatic distribution which must be irradiated. Theoretically, the entire esophageal bed, from the supraclavicular region to the celiac axis, would need to be covered. Treatment of such a large field would carry a risk of sig-
significant morbidity. Furthermore, the presence of the stomach or a colonic interposition in the radiation field, as would necessarily be the case postoperatively, is likely to further increase radiation toxicity. For these reasons, in the absence of randomized data supporting this approach, the use of postoperative radiation therapy cannot be routinely recommended.

Preoperative chemotherapy

Treatment failure of conventional surgical or radiation therapy in local-regional esophageal cancer is often on the basis of distant as well as local recurrent disease. Indeed several autopsy series performed on patients who died of esophageal cancers show frequent evidence of disseminated disease at or soon after the time of diagnosis. Three such studies have been reported, all of which involved patients with a relatively short duration of illness prior to death [17–19]. Despite median survivals of 4 and 6 months in two of the studies, and inclusion of a large number of patients with deaths in the immediate postoperative period in the other study, all three studies reported that a majority of patients had metastatic cancer at autopsy (see Table 1). It is thus reasonable to assume that a large percentage of patients who present with symptomatic disease have disseminated cancer at the time of presentation, and that effective systemic treatments might improve survival rates.

Further justification for the investigation of preoperative chemotherapy has been provided by a random assignment trial comparing preoperative chemotherapy with preoperative radiotherapy [20]. Patients with operable epidermoid carcinoma of the esophagus were randomized to preoperative treatment with 5500 cGy of radiation or two cycles of cisplatin, vindesine, and bleomycin. The major endpoints of this investigation were objective response rates, surgical outcome, and recurrence patterns. Objective response rates (64% and 55%) and operability rates (77% and 75%) were similar for the radiation and chemotherapy groups respectively, as were the resectability rates (65% and 58%) and operative mortality rates (13.5% and 11.1%). A comparison of survival was not possible since a postoperative crossover was permitted. The median survival for the entire group (96 patients) was 11 months. The most important finding of this study was that chemotherapy, which has the potential to address the problem of metastatic disease, also appeared to be as effective as radiation therapy in terms of control or local-regional disease.

Other theoretical advantages to preoperative chemotherapy have been proposed [21]. Laboratory data exist which indicate a benefit to preoperative administration of chemotherapy in an animal model [16]. Furthermore, use of chemotherapy early in the course of a disease results in treatment when the tumor burden is relatively low. This may decrease the incidence of spontaneous emergence of drug-resistant tumor cell populations [22]. Treatment in the preoperative, rather than the postoperative period, also permits an assessment of tumor response, either by barium swallow, CT scan, or by the investigational technique of endoscopic ultrasound [23].

While preoperative chemotherapy has been studied for over 15 years, the vast majority of studies have been single arm, uncontrolled trials (see Table 2). As such, these trials have been able to establish the feasibility, but not the efficacy, of this approach. Median survivals, when reported, have ranged from 17–24 months [21]. The median follow-up in the majority of these studies is quite short, resulting in a paucity of meaningful survival data. One study involving 34 patients with local-regional disease treated with cisplatin, vindesine, and bleomycin has been followed out to a minimum follow-up of 7 years [24]. The 5-year survival rate was 17.6%, and no relapses were noted after 3½ years.

Few randomized trials have been reported. In one small trial, 39 patients were randomized to receive either pre- and postoperative cisplatin, vindesine, and bleomycin, or surgery alone. Operative morbidity was actually slightly higher in the surgery only group (47% versus 29%). The median survival for both treatment groups was 9 months. The authors pointed out that patients with responses to chemotherapy had longer survivals than either non-responders or those not receiving chemotherapy. They also noted that those patients with less advanced disease were more likely to respond to chemotherapy. Thus, the patients with less advanced disease were, not surprisingly, more likely to survive longer. Given the small number of patients involved, no deduction of a survival advantage for chemotherapy can be drawn from this study.

Two large randomized trials are underway which can be expected to define the role, or lack thereof, of preoperative chemotherapy using currently available regimens. A three arm study by the European Organization for the Statistical Study of Esophageal Diseases

Table 1. Sites of metastases esophageal cancer failure pattern: Autopsy data.*

<table>
<thead>
<tr>
<th>Sites of disease (%)</th>
<th>Anderson*</th>
<th>Bosch</th>
<th>Mandard*</th>
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<tr>
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<tr>
<td>Distal only (%)</td>
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</tr>
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<td>Liver</td>
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<tr>
<td>Lymph nodes</td>
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<td>Adrenal (%)</td>
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<td>12</td>
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</tr>
<tr>
<td>Trachea-bronchus</td>
<td>17</td>
<td>33</td>
<td>16</td>
</tr>
</tbody>
</table>

* Autopsy performed a median of 4 h or 6.3 c months from diagnosis.

(OESO) is comparing a preoperative chemotherapy arm (cisplatin, vindesine and bleomycin) against a postoperative radiation therapy arm, and a surgery only arm. This study has reached its accrual targets and an analysis of the data is underway. A second trial, the U.S. National Intergroup Trial, involving several cooperative groups, is randomizing patients to receive either surgery alone or three preoperative and two postoperative cycles of cisplatin and fluorouracil. This trial is now actively accruing patients.

It must be noted that while preoperative chemotherapy is under active investigation, there are at present no randomized trials confirming a survival advantage for patients treated by this approach; preoperative chemotherapy should therefore be regarded as an investigational treatment which would not, at present, be appropriate outside of the context of a clinical trial.

**Concurrent chemotherapy and radiotherapy without surgery**

Although radiation therapy is an acceptable standard treatment for local-regional esophageal cancer, the long term survival results with this treatment alone are, as discussed previously, quite unsatisfactory. Several investigators have attempted to improve on these results by combining radiotherapy with chemotherapy. A number of uncontrolled phase II trials have been reported. As is the case with preoperative chemotherapy, such trials have as their endpoints tolerance and preliminary assessment of efficacy, but are not definitive tests of superiority in comparison to standard therapy.

In one such trial, 30 patients with stages I and II disease were treated with mitomycin, 5-fluorouracil, and 6000 cGy of radiation. The radiation was administered over 6–7 weeks. The four day chemotherapy cycle was repeated starting on day 29 [25]. Twenty patients with stage III or IV disease received palliative treatment with the same chemotherapy plus 5000 cGy of radiation. The median survival in the palliative group was 8 months. The 2 and 5 year survival rates in the stage I and II patients were 47% and 32% respectively, although in a subsequent long-term follow-up report, the 3-year and 5-year survival rates had decreased to 29% and 18% respectively, with median survival of stages III and IV patients of 9 months and 8 months respectively [5].

In another phase II trial, a complex regimen involving cisplatin, 5-fluorouracil and concurrent radiation to 3000 cGy, followed by cisplatin and 5-fluorouracil, followed by mitomycin and bleomycin, followed by a boost of 2000 cGy of radiation, was administered to 20 patients with squamous cell esophageal cancer [26]. The toxicity of this four drug regimen was felt to be prohibitive. The median survival for the 20 patients was 22 months.

A third trial employed two courses of cisplatin and 5-fluorouracil given concurrently with two 5-day courses of split-dose radiation therapy. Each of the two radiation courses was 2000 cGy [27]. Toxicity was acceptable. Twenty-five of the 35 patients in the trial had a biopsy-documented complete response. The overall median survival was 17 months. The median survival for stage I and II patients was 28 months.

Two of the earlier randomized trials which compared chemotherapy plus radiation to radiation alone utilized either single agent bleomycin or single agent methotrexate [28, 29]. Neither of these studies showed a difference between the two treatment arms, a finding which is not surprising given the limited activity of the chemotherapy used. A small, randomized trial comparing radiation plus concurrent 5-fluorouracil, mitomycin C, and bleomycin to radiation alone in patients with stage II squamous cell carcinomas also failed to show a significant difference between the two arms, either in terms of response rates, duration of responses, or overall survival, however this trial probably involved too
few patients to permit detection of modest differences [30].

In a non-randomized, retrospective study, 65 patients were treated with either radiotherapy alone (5600 to 6100 cGy over 6–7 weeks) or combined therapy with 4140 to 5040 cGy of radiation with 4 days of infusional 5-fluorouracil, 1000 mg/m²/day, on weeks 1, 4 and 8, mitomycin 10 mg/m² by bolus at the beginning of weeks 1 and 8, and cisplatin, 75 mg/m², given on week 4 [31]. Patients in the chemotherapy arm then received maintenance chemotherapy with methotrexate 200 mg/m² followed by leucovorin rescue, and 5-fluorouracil 600 mg/m², on weeks 10, 12, and 14. Endoscopic biopsy-documented complete response rates were significantly higher in the group receiving chemotherapy (77% versus 30%, p = 0.0001). Survival rates for the group receiving chemotherapy were better at one year (53% versus 27%) and two years (29% versus 13%, p = 0.023). The toxicity of the combined-modality arm was acceptable.

Two large, randomized trials of combined radiotherapy and chemotherapy versus radiotherapy alone have now been reported, in abstract form, which appear to show an advantage for the combination over radiation therapy alone. The Eastern Cooperative Oncology Group has reported its interim results of a study comparing radiotherapy alone with radiotherapy plus mitomycin C and fluorouracil in patients with squamous cell cancer of the esophagus [32]. The study is somewhat difficult to interpret because it allowed surgery at the discretion of the treating physician. Of 135 patients entered, 118 were eligible and had follow up data available. Of these 118, 80 had stage II disease and 38 had stage I disease. All patients received an initial treatment of 4000 cGy, and then had the option of undergoing surgical evaluation. Patients not undergoing surgery received an additional 2000 to 2600 cGy. Those patients randomized to combination therapy received chemotherapy beginning on day 2 of radiation, with a bolus of mitomycin C 10 mg/m², and a 4 day infusion of 5-fluorouracil at 1000 mg/m²/day. The 5-fluorouracil was repeated beginning on day 28.

The authors did not state how many patients went to surgery, or what criteria were used in this decision. Of the patients not operated on, the overall median survival was 11 months, with median survivals for patients with radiation only versus radiation and chemotherapy of 9.0 and 14.9 months, respectively. This difference was reported to be statistically significant, with P = 0.03 after accounting for the factors used in the randomization procedure. It should be noted that since this report has only appeared in abstract form thus far, the detailed data are not available for review.

In a second random assignment study, an intergroup trial performed by the Radiation Therapy Oncology Group, the Southwest Oncology Group, and the North Central Cancer Treatment Group, randomized patients to 6400 cGy of radiation alone, or to 5000 cGy given with two concurrent courses of cisplatin and 5-fluorouracil and followed by two additional cycles of the same chemotherapy [33]. An analysis has been carried out on the first 120 patients. The 12 and 24 months survival rates were 35% and 10% respectively for the radiation-only group, and were 52% and 42% for the chemotherapy plus radiation group (log rank p = 0.0017). Based on these findings, the radiation-only arm of the study has been closed, and accrual has continued on the combined-modality arm.

These randomized trials appear to present a strong argument in favor of concurrent chemotherapy and radiotherapy over radiotherapy alone in the treatment of local-regional esophageal cancer. It must be emphasized, however, that these studies have only been reported in abstract form. Although these reports are encouraging, determination of the role of concurrent chemotherapy and radiotherapy in the routine management of esophageal cancer must await a full analysis of the data when they are presented in their final form.

Preoperative chemotherapy and radiotherapy

Given the encouraging preliminary data seen with concurrent chemotherapy and radiotherapy, the concept of combining these two modalities in a preoperative setting would appear to be promising. Thus far, however, this has not proved to be a rewarding approach.

As in other combined-modality approaches, the majority of work in this area is in the form of single arm, uncontrolled trials (see Table 3). Several of the earlier reports of preoperative chemotherapy and radiotherapy came from investigators at Wayne State University in Michigan. A report of 55 patients treated with mitomycin C, 5-fluorouracil, and 3000 cGy preoperatively, and followed by further chemotherapy and radiotherapy if viable tumor was found in the resected specimen, showed a median survival of approximately 18 months [34]. A subsequent pilot trial from the same institution utilized cisplatin, 5-fluorouracil, and 3000 cGy of concurrent radiation [35]. Of the 21 patients entered, 15 came to operation and 5 were found to have a pathologically-documented complete response. Again, the median survival was 18 months. The authors reported a median survival of 24 months in the 5 patients with complete responses, however the bias inherent in this sort of subset analysis is such that one must be very cautious in interpreting this observation. None of the patients in this study remained disease-free; distant tumor recurrence was noted in all of these patients at 30–60 months, and all have subsequently died [26]. A large phase II trial of the same regimen in 41 patients by the Radiation Therapy Oncology Group demonstrated a median survival of 13 months [36]. A still larger trial by the Southwest Oncology Group, utilizing a slightly lower dose of cisplatin (75 mg/m²), showed an overall survival of 12 months [37].

A more recent phase II trial involving 43 patients
Advances in radiation technology, with improvedfractionation techniques and three dimensional treatmentplanning, may improve the efficacy of this modality, either alone or in combination with other treatmentmodalities.

Obviously there is much room for improvement, and most questions regarding optimal therapy for local-regional esophageal cancer remain unanswered. Surgery remains one standard treatment, as does radiotherapy. If the preliminary results are confirmed, then chemotherapy plus concurrent radiotherapy will supplant at least radiotherapy in this regard. The ongoing intergroup trial in the United States and similar random assignment trials planned in the United Kingdom will further address the question of whether systemic plus regional therapy is superior to regional therapy alone. As data become available from these trials, a number of important questions should be answered.

Table 3. Selected studies of chemotherapy plus RT prior to surgery.

<table>
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<tr>
<th>Cell type</th>
<th>RT dose</th>
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<th>Concur</th>
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<th>Op</th>
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Abbreviations: MTX = Methotrexate; BLE = Bleomycin; Concur = Concurrent RT; DDP = Cisplatin; FU = Fluorouracil; Y = Yes; Op = Operability (%); Res = Resection (%); N = No; E = Epidermoid; A = Adenocarcinoma; B = Both.


References


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