Neoadjuvant therapy for esophageal cancer

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Abstract

Esophageal cancer is increasing in incidence more than any other visceral malignancy in North America. Adenocarcinoma has become the most common cell type. Surgery remains the primary treatment modality for locoregional disease. Overall survival with surgery alone has been dismal, with metastatic disease the primary mode of treatment failure after an R0 surgical resection. Cure rates with chemotherapy or radiation therapy alone have been disappointing. For these reasons, over the last decade multi-modality treatment has gained increasing acceptance as the standard of care.

Use of chemotherapy with or without radiation therapy before surgery has several theoretical benefits. It may improve baseline dysphagia, the most common symptom on presentation. It can help downstage the tumor, which may increase resection rates, and can treat micro-metastatic disease that is not detected on imaging studies. It has the potential to indicate the biologic behavior of the tumor by its response to treatment that may help guide further therapy.

The role of multi-modality treatment as a way to achieve higher long-term survival rates has been debated for many years. The roles of chemotherapy and radiation therapy to improve surgical results remain controversial; randomized trials have shown mixed results. This review will examine the data and survival rates for using pre-
operative chemotherapy and radiation therapy, alone or in combination, in the management of localized esophageal cancer.

NEOADJUVANT CHEMOTHERAPY

In a study by Boonstra et al., 169 patients with squamous cell cancer were randomized to 2-4 cycles of cisplatin and etoposide followed by surgery or surgery alone. Median overall survival in the two groups was 16 and 12 months respectively. The 5-year survival in the chemotherapy group was 26% vs 17% in the surgery alone group (P = 0.03, hazard ratio 0.71; 95% CI: 0.51-0.98). Contrary to this study result, a large North American Intergroup 113 trial failed to show a survival benefit for three cycles of pre-operative cisplatin/5-FU followed by surgery and two additional cycles of cisplatin/5-FU compared to surgery alone. Both squamous and adenocarcinoma patients were included. With a study size of 440 patients, overall survival in each group was 20% and there was no benefit of chemotherapy seen in resection rates, local failure, or distant metastasis.

In a much larger study by the Medical Research Council Oesophageal Cancer Working group, 802 patients were randomized to two cycles of cisplatin/5-FU followed by surgery vs surgery alone. Median and 2-year survivals were improved in the chemotherapy group (16.8 mo vs 13.3 mo; difference 3.5 months; 95% CI: 0.0-6.9, and 43% vs 34% difference 9%; 95% CI: 3.14, respectively). The curative resection rate was improved marginally from 55% to 60%. The MAGIC trial, performed in the United Kingdom, further reinforced the findings seen in the Medical Research Council study. A total of 503 patients with distal esophageal, GE junction and gastric adenocarcinoma were randomized to three cycles of pre and post-operative cisplatin/5-FU/epirubicin or surgery alone. Overall survival in the chemotherapy group was significantly better (36% vs 23%, P = 0.009), but fewer than one third of the patients in this study had distal esophageal adenocarcinoma. In a French study of 224 patients randomized to 2-3 cycles of preoperative cisplatin/5-FU followed by surgery vs surgery alone, there was a significantly improved R0 resection rate (84% vs 73%, P = 0.04), 5-year disease free survival (34% vs 21%, P = 0.003), and 5-year overall survival (38% vs 24%, P = 0.02) following chemotherapy.

The data published in these studies are quite heterogeneous. Some studies have both squamous and adenocarcinoma patients while some have only adenocarcinoma patients. The chemotherapy drugs and regimens vary between studies as well. In a meta-analysis of 12 randomized trials in which pre-operative chemotherapy was used, the 5-year overall survival benefit was only 4%. The benefit was somewhat smaller for squamous cell cancer compared to adenocarcinoma (4% vs 7%). Thus, the available data do not suggest that the use of neoadjuvant chemotherapy significantly improves survival.

NEOADJUVANT RADIATION THERAPY

In a trial of 96 patients by Kelsen et al., patients were assigned to preoperative radiotherapy or chemotherapy. The morbidity and mortality of surgery following preoperative treatment was no different compared to historical controls of surgery alone but there was no survival benefit of preoperative treatment. Another randomized trial of 176 patients comparing preoperative radiation (20 Gy in 10 treatments) followed by surgery vs surgery alone showed no benefit of radiotherapy with overall 5-year survival of 13%. In a Scandinavian trial of 186 patients, Nygaard et al. showed an improved 3-year survival in patients receiving preoperative radiotherapy compared to patients undergoing surgery alone or chemotherapy and surgery.

A meta-analysis has not shown a statistically significant survival benefit for preoperative radiation. At a median follow-up of 9 years, the survival benefit at 2 and 5 years was 3% and 4% respectively (P = 0.062). Thus neoadjuvant radiation therapy alone cannot be advocated for the management of esophageal cancer.

NEOADJUVANT CHEMORADIOThERAPY

(COMBINED THERAPY, TRIMODALITY THERAPY)

Neither preoperative radiation therapy nor chemotherapy alone in the neoadjuvant setting have been proven beneficial based on the trials performed. This may be related to the low complete pathologic response rates, mostly between 2.5%-4%. The improvement in R0 resection and overall survival has been limited as well. Most patients who undergo surgical resection die from distant metastatic disease in spite of an R0 resection. Considering these results and for the reasons listed earlier in this review for using neoadjuvant therapy, combination therapy with all three modalities has been utilized to try to improve overall outcomes. We will first review the studies looking at trimodality therapy vs surgery alone.

Trimodality therapy vs surgery alone

Bosset et al. randomized 282 patients to preoperative cisplatin and concurrent radiation or surgery alone. Although the curative resection rate was higher with combined therapy (81% vs 69%), disease-free survival was improved (HR 0.6, 95% CI: 0.40-0.9, P = 0.003), and risk of local recurrence decreased (HR 0.6, 95% CI: 0.40-0.9, P = 0.01), there was no difference in overall survival. This may at least in part be due to higher than expected treatment related mortality in the chemo-radiation arm (12% vs 4%). This study only included patients with squamous cell cancers, and radiation was given using a split-dose technique.

Burmeister et al. in an Australian study randomized 256 patients to one cycle of cisplatin/5-FU and radiation
followed by surgery or to surgery alone. R0 resection was achieved in 80% of the patients in the combined therapy group vs 59% in the surgery alone arm. However, the overall survival was no different between the two groups. Patients with adenocarcinoma had a decreased rate of complete pathologic response and were more likely to have disease progression during the follow-up period.

In a study from the University of Michigan, 100 patients were randomized to preoperative cisplatin/5-FU/vinblastine plus radiation or to surgery alone. There was a significant decrease in the rate of local recurrence with combined therapy (19% vs 42%, $P = 0.03$) and a trend towards improved survival at 3 years (30% vs 16%, $P = 0.15$). In an Irish study of 113 patients, Walsh et al. showed a significant improvement in overall survival at 3 years (32% vs 6%) with preoperative cisplatin/5-FU/radiation followed by surgery vs surgery alone. All patients in this study had adenocarcinoma but the extremely poor 3-year survival in the surgery alone arm (6%) could not be explained. In 2012, a multi-institutional phase III study (CROSS trial) evaluated the benefit of induction therapy using carboplatin/taxol/41Gy radiation vs surgery alone. Only a quarter of the patients had squamous histology. There was an anastomotic leak rate of 22%-30% in each arm. Median survival was 49 mo in the combined therapy arm compared to 24 mo in the surgery arm ($P = 0.003$). The overall 5-year survival was much improved in the combined therapy arm (47% vs 34%, $P = 0.03$). Patients with squamous histology derived a larger benefit. An updated analysis of this group of patients showed a lower local recurrence rate (34% vs 14%, $P < 0.001$) and lower risk of peritoneal carcinomatosis (14% vs 4%, $P < 0.001$) following neoadjuvant chemoradiotherapy and that squamous cell carcinoma was an independent prognostic variable in the surgery alone group.

**Neoadjuvant chemoradiation vs neoadjuvant chemotherapy alone**

Stahl et al. reported their data of 120 patients with T3 or higher and/or node positive patients who were randomized to preoperative cisplatin/5-FU/leucovorin followed by surgery vs cisplatin/5-FU/leucovorin followed by chemoradiotherapy with cisplatin/etoposide and then surgery. Tri modality patients had a higher rate of pathologic complete response (16% vs 2%, $P = 0.03$) and node-negative status (64% vs 37%, $P = 0.01$). The overall 3-year survival was not statistically different in the two groups with a median overall survival of 32.8 mo vs 21.1 mo ($P = 0.14$).

In a recent meta-analysis of 10 randomized trials of trimodality therapy vs surgery alone and 8 trials of preoperative chemotherapy vs surgery alone, trimodality therapy was associated with a 13% benefit in survival at 2 years, both in squamous and adenocarcinoma. Preoperative chemotherapy alone translated to a 7% benefit in survival at 3 years, more in adenocarcinoma than in squamous cell cancer. Thus, these data suggest a synergistic benefit using neoadjuvant chemotherapy plus radiotherapy in the management of esophageal cancer.

**CONCLUSION**

The three mainstays of treatment for esophageal cancer-surgery, chemotherapy, and radiation therapy result in poor overall survival and high relapse rates when used alone. Preoperative combination therapy offers several theoretical advantages but for stage 1 and 2 esophageal cancers, there is, as of now, no convincing evidence that neoadjuvant chemoradiation is of any benefit. Neoadjuvant chemoradiotherapy achieves the highest complete pathologic response rates, R0 resection rates, and improves 3-5 years survival rates in patients with locally advanced esophageal cancer. The addition of neoadjuvant radiotherapy to preoperative chemotherapy may facilitate a better complete surgical resection via its effect on the periphery of the tumor. Squamous cell cancer and adenocarcinoma appear to have similar disease-free and overall survival rates following neoadjuvant chemoradiotherapy. Further randomized, prospective trials will be required to build on these early studies to try to improve the prognosis of patients with this terrible disease.

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