



# Locoregional and oligometastatic recurrence of esophageal cancer – what are the management strategies?

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Over the past few decades, prognosis of esophageal cancer has improved with the advent of multimodality treatment and refinement of surgical techniques and perioperative care. A 5% 5-year survival across all stages was quoted in the 1960s which has evolved to a 20% all stage 5-year survival today (1). Clearly the reality of esophageal cancer is still grim and there is progress to be made. Within the cohort of patients that are operable, nearly 50% of patients will recur (2). Majority of recurrences after treatment are distant/hematogenous metastases highlighting the need for improved systemic control. Local and locoregional recurrence can account for approximately 20–30% of cases. The objective of this article is to discuss the optimal management of loco-regional and isolated distant recurrence after definitive treatment for esophageal cancer.

The categorization of esophageal cancer recurrence is diverse in the literature which has contributed to the challenges of understanding and contrasting the outcomes of recurrence treatment (3). A local recurrence is often synonymous with anastomotic or perianastomotic recurrence. However, the term “regional recurrence” has varied uses. Firstly, regional recurrence can vary according to primary tumor location. Furthermore, there has been significant overlap between non-regional lymph nodes, and single station metastases. Oligometastatic disease is also diversely defined from single station solid organ metastases to multiple metastases with or within bony involvement (4). A unified approach to esophageal cancer recurrence categorization is required.

## Local/anastomotic recurrence

One of the largest series on re-resection after esophageal

cancer recurrence is from Schipper and colleagues (5) studying a cohort of 27 patients. Adenocarcinoma accounted for 90% of the pathology, 56% had Ivor Lewis esophagectomy as their original surgery with 44% having pre-operative chemoradiotherapy. Recurrence was associated with symptoms in 74% and median disease-free interval from esophagectomy was 19.4 months (range, 2.5–170 months). Completion gastrectomy and partial esophagectomy with colon interposition occurred in 10 (37%) of patients, resection of anastomosis with esophagogastrectomy in 9 (33%) patients, and an overall 56% R0 resection was achieved. In 8 patients' unresectable disease was found and only a biopsy was completed. Post-operative course was remarkable for 7.4% mortality, 26% anastomotic leak rate, 20 days (range, 8–64 days) length of stay and 37% returning to OR for complications. Despite the increased morbidity associated with the postoperative course, patients who received complete resection had a 1-, 2- and 5-year survival of 62%, 44% and 35% respectively. Age, preoperative chemoradiation, presence or absence of symptoms, complication and site of recurrence did not affect survival. However, disease-free interval greater than two years was associated with longer survival after recurrence. Re-resection in this cohort was technically challenging due to scarring and previous radiation however with proper patient selection, surgery for an anastomotic recurrence can yield meaningful survival.

Management in squamous cell carcinoma recurrence can also result in favorable long-term outcomes with the proper selection. Bao *et al.* studied 20 anastomotic recurrences in patients who received upfront surgery for squamous cell carcinoma (6). These occurrences were treated with

chemoradiation (60 Gys) with a median follow up of 34 months. A remarkable three-year survival of 74% was observed. The authors also studied the same treatment regimen for regional lymph nodes with the resultant 44% overall three-year survival. Better prognosis for anastomotic occurrence can be attributed to earlier detection due to symptoms and, possibility of the new primary among other factors. Although overall striking findings the study included a very specific population, subjecting it to selection bias. The small cohort number and shorter follow-up times are additional limitations. Rescue with chemoradiation for locoregional recurrence of squamous cell cancer in the literature is still quite variable. Three-year survival rates between 15–51.3% have been reported and therefore prognosis remains guarded (7).

### Regional recurrence

Regional lymph node recurrence in squamous cell cancer is not an uncommon scenario. A study of 24 recurrences, 17 after esophagectomy and 7 after definitive chemoradiation reported differential outcomes between the two cohorts (8). Surgical lymphadenectomy after initial esophagectomy yielded a 3-year disease-free interval of 51.5%, and a 3-year overall survival of 75.5%. Interestingly, lymphadenectomy after initial chemoradiation had a dismal prognosis with median disease free survival of 2 months and overall survival of 15 months. Limitations of this study include its retrospective nature, a selection bias for surgical patients and varying adjuvant treatments. However, it does suggest that surgery for cervical lymph node recurrence for squamous cell carcinoma is a reasonable treatment modality.

Depypere *et al.* in one of the largest studies on esophageal cancer recurrence analyzed 1,754 patients with an overall recurrence of 43.7% in an adenocarcinoma predominant cohort (9). Locoregional recurrence to one lymph node station was associated with an overall 5-year survival of 23.7%. When focusing on isolated locoregional recurrence or a solitary organ metastasis 25 patients received surgical therapy with or without systemic therapy, with a 5-year survival of 49.9% (median 54.8 months) after diagnosis of recurrence. When surgery was not feasible, chemoradiotherapy still appeared to be superior to chemotherapy alone (27.0% *vs.* 4.6% 5-year survival respectively). Interestingly in this cohort anastomotic recurrence was associated with a bleak 12.5% 5-year survival. The data did not offer details, but this finding in

part could be attributed to no surgical management for all the anastomotic recurrences.

### Isolated single organ recurrence

Isolated single organ recurrence after definitive treatment for esophageal cancer is a rare event. Several small series have been published on isolated lung metastases. Overall survival varies from 18–37 months across studies that primarily performed wedges and segmentectomies as the vast majority of their resections (10–12). A predictive factor for poor prognosis remained a disease-free interval of less than 12 months possibly reflecting insufficient local control and aggressive tumor biology. Furthermore, a primary squamous cell carcinoma of the lung versus recurrence from an esophageal cancer was challenging for some series to distinguish which may contribute to the favorable outcomes.

Ghaly and colleagues studied 241 esophageal cancer recurrences focusing on those managed definitively (with surgery or chemoradiation) for oligometastases (13). The study's aim was to search for predictors of survival after definitive management. In a group of anastomotic, regional lymph node and isolated distant metastases—the group found a 24.5 months overall survival with surgery and 28 months with chemoradiation. Several independent variables were studied in the model but a time to recurrence of less than 12 months was once again the only predictive factor in improved post recurrence survival.

### Conclusions and future direction

Optimal management of locoregional and isolated distant recurrence of esophageal cancer remains controversial. But with a well selected patient cohort definitive treatment with surgery or chemoradiation is a valid strategy. Treatment and outcomes will vary according to tumor factors (histology/biology, location and time of recurrence), patient factors (functional status) and previous treatment (neoadjuvant chemoradiation).

There is a need to standardize classification for esophageal cancer recurrence to obtain accurate clinical assessment and compare outcomes in the literature. Future prospective studies that focus on recurrences after a disease-free interval of 12 months, that evaluate different therapeutic options and incorporate quality of life after treatment would advance the field in this topic.

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## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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