

ROLE OF RADIOTHERAPY IN OPERABLE OESOPHAGEAL CANCER

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Abstract

External beam radiotherapy with concurrent chemotherapy has been established as one of the primary curative treatment modalities for oesophageal cancer. Technological improvements in imaging have allowed more appropriate selection of patients for curative radiotherapy. An evolving role of preoperative chemo-radiation therapy prior to surgery is being established, with more routine use in the management of operable oesophageal cancer. This article will review the current clinical approach to radiation therapy treatment of operable oesophageal cancer.

Oesophageal cancers occur throughout the oesophagus, within the cervical region beginning below the cricopharyngeal muscle and throughout the thoracic oesophagus. Gastro-oesophageal junction tumours have been included in trials treating both oesophageal cancers and gastric cancer. The most common histological subtypes are squamous cell carcinomas (SCC) and adenocarcinomas, with the former typically occurring in the upper oesophagus and the latter in the lower oesophagus. Despite the different histology, both cancers share a fairly poor five year survival rate of approximately less than 50% once the muscularis propria is involved, and less than 40% in node positive disease.

Recently the American Joint Committee on Cancer published the Cancer Staging Manual (7th edition), with a revision of the TNM staging of oesophageal cancers, differentiating the staging of SCC from adenocarcinomas.¹ The main changes included the sub-classification of T4 disease into operable and inoperable groups, the N stage based on the number of lymph nodes involved from cervical to celiac axis and the M stage based on distant metastases alone. Histological grade is now included in adenocarcinomas, and the staging of adenocarcinomas involving the proximal 5cm of gastric cardia and invading into the gastro-oesophageal junction (eg. Siewert III) are similarly staged as adenocarcinomas of the oesophagus. These changes reflect the changing treatment paradigm of oesophageal cancers.

The main primary curative treatment used for cervical and upper thoracic oesophageal cancers is chemo-radiation therapy, with surgery for cervical oesophageal cancers typically requiring a laryngopharyngoesophagectomy, however for lower thoracic oesophageal cancers multiple approaches to treatment are currently used in clinical practice including surgery alone, chemo-radiation therapy, preoperative chemotherapy and preoperative chemo-radiation therapy.

For early operable oesophageal cancers (eg. T1/2 N0), the main treatment modality used is surgery alone, with five year survival typically >60% at five years.¹ For patients with inoperable T1 or T2, node negative cancers, chemo-radiation therapy or radiation therapy alone can also be used curatively with reasonable survival rates at five

years of 30-70%.²⁻⁵ For more advanced disease (>T3N0) where survival rates are typically <30% at five years, chemo-radiation therapy has a definite role in the curative treatment. The following discussion in the rest of this article relates to these locally advanced operable cancers.

Definitive radiation therapy for operable oesophageal cancer

The role of radiation therapy in oesophageal cancer has been evolving since the 1980s. In 1985, the Radiation Therapy Oncology Group 85-01 trial randomised patients to radical radiation therapy alone compared to concurrent chemo-radiation therapy (chemo-radiation therapy).⁶ This established superior outcomes of chemo-radiation therapy over radiation therapy alone. Despite the chemo-radiation therapy arm using a lower total dose of radiation (ie. 50 Gy in 25 treatment fractions versus 64 Gy in 32 treatment fractions) there was an improved overall survival at five years of 26% and 0% for chemo-radiation therapy and radiation therapy respectively. No statistical significant differences (p=0.15) in survival based on histology were reported after chemo-radiation therapy at five years. The benefits of chemo-radiation therapy included reduced rates of distant metastases as first site of failure (30% for radiation therapy v 16% for chemo-radiation therapy) and reduced risk of local failure (65% for radiation therapy and 46% for chemo-radiation therapy).

Although, theoretically, the use of higher doses of radiation therapy in combination with chemotherapy should improve the chance of tumour cure, the Intergroup 0123 randomised control trial showed no improvement in local control or survival when escalating radiation therapy dose to 64.4 Gy, as compared to 50.4 Gy with cisplatin and 5-fluorouracil (5-FU) based chemo-radiation therapy.⁷ More toxicity was observed when using higher radiotherapy doses, with 10% treatment-related deaths being observed on the high dose arms as compared to 2% on the lower dose arm. Similarly, in the cervical oesophagus a relatively large retrospective study from Canada has shown no improvements in survival when comparing radiotherapy to 70 Gy in 2 Gy fractions with high dose cisplatin, compared to lower dose radiotherapy 54 Gy in 2 Gy fractions with 5-FU and mitomycin C or cisplatin.⁸ Location of first site of failure was loco-regional in 71% and

the reported local relapse-free survival rates at two years were similar (48% v 46%). The five year survival of patients treated curatively was 28%. Currently, radiation therapy doses in the range of 50 to 66 Gy are used to treat cervical oesophagus SCC, however 50 Gy is used throughout the thoracic oesophagus due to dose limiting toxicity.

The role of histology in differentiating best treatment approaches is less clear from the published literature. In a series of 1059 surgically resected oesophageal cancers, Siewert et al analysed potential prognostic factors.⁹ In addition to surgical margin resection status and TNM staging, the histology of adenocarcinomas was associated with a better prognosis following surgery. This translated to an overall survival of resected adenocarcinomas and SCC at five years of 42% and 30% respectively. However, adenocarcinomas more commonly occur in the distal oesophagus compared to SCC occurring usually in the mid to upper oesophagus. Cancers in the mid and upper oesophagus typically are situated closer to critical vascular and other normal structures, making surgery technically more difficult. A recent SEER database review on 4752 patients with oesophageal cancer has not shown adenocarcinomas to be a significant predictor for outcome, and this is in keeping with the randomised trials of radiation therapy for treatment of oesophageal cancer discussed previously.^{6,10} Comparing adenocarcinomas and SCC, the respective five year survival for patients treated with radiation therapy alone were 18% and 18%, for preoperative radiation therapy 34% and 33%, for surgery alone 14% and 13%. This indicates that histological subtype does not predict for poorer response to radiation therapy and that it should not necessarily influence the decision on the most appropriate treatment modality a patient should receive. Therefore, factors such as risk of morbidity and the technical feasibility of treatment are the most important factors when considering patients for surgery and/or radiation therapy.

Currently the relatively high loco-regional failure rates with chemo-radiation therapy alone, of approximately 50%, remain suboptimal, particularly given the lack of impact higher doses of radiation have so far provided. This has led to increasing consideration of multimodality treatment approaches in operable oesophageal cancers.

Preoperative radiotherapy

Preoperative radiation therapy alone (without chemotherapy) has had minimal impact on improving outcomes of patients with operable oesophageal cancer. A Cochrane review of 1147 patients' individual data from five randomised trials has shown that there is potentially a small (4% at five years) non-statistically significant benefit ($p=0.06$) of the use of preoperative radiotherapy.¹¹ Eighty-nine percent of these patients analysed had SCC of the oesophagus. Radiotherapy doses ranged from 20 Gy in 10 fractions to 40 Gy in 10 fractions.

The use of preoperative chemo-radiation therapy has been gaining more favour recently. Individually, randomised control trials have been fairly small and inconsistently showing if there were benefits of the addition of chemo-radiation therapy to surgery.¹²⁻¹⁹ In 2004, a meta-analysis of six randomised control trials showed a potential benefit

of preoperative chemo-radiation therapy by improving survival at three years.²⁰ The odds ratio for survival at three years was 0.53 [95% CI 0.31-0.93], however this was at the expense of increased postoperative mortality with an odds ratio of 2.1 [95% CI 1.18-3.73]. This survival benefit was more pronounced and statistically significant in adenocarcinomas than SCC. A more recent meta-analysis has analysed both the potential benefits of preoperative chemotherapy and chemo-radiation therapy.^{21,22} In this analysis by the Australasian Gastro-Intestinal Trials Group, 12 preoperative chemo-radiation therapy and nine preoperative chemotherapy trials were analysed, including another two trials comparing preoperative chemo-radiation therapy to chemotherapy. In total, 4188 patients with oesophageal or oesophagogastric junction carcinoma were included. Typical prescribed radiotherapy doses in the trials reported ranged from 20 Gy in 10 fractions, up to 50.4 Gy in 28 fractions, all combined a platinum compound, usually cisplatin and commonly 5-FU chemotherapy. A significant benefit in survival was seen by the addition of preoperative chemotherapy and chemo-radiation therapy. The benefit for SCC and adenocarcinomas was similar for the addition of chemo-radiation therapy (hazard ratio 0.78 [0.70-0.88] and 0.80 [0.68-0.93] respectively). Additionally, the use of preoperative chemo-radiation therapy may potentially have a larger benefit than chemotherapy alone (hazard ratio 0.88 [0.76-1.01] $p=0.07$) and the 30 day perioperative mortality was not associated with the use of neoadjuvant treatment. From trials comparing preoperative chemo-radiation therapy and surgery alone, the median 30 day perioperative mortality rate was 6.9% [range 0%-17.2%) and 3.8% (range 0%-18.8%) respectively. For the trials comparing preoperative chemotherapy and surgery alone, these respective values were 6.8% [range 2.1% - 14.7%] and 5.6% [range 0%-10.0%]. The comparison of preoperative chemo-radiation therapy and chemotherapy were indirect and therefore prone to bias, however it does indicate a potential benefit for preoperative chemo-radiation therapy and the need for further randomised trials.

The optimum radiation dose in preoperative chemo-radiation therapy is not established. Concerns about using higher doses of radiation therapy relate to the potential increased risks of post-operative complications including anastomotic leaks. A recent randomised trial reported by Tepper et al, has not shown a significant increased morbidity with higher dose (50.4 Gy) radiation therapy.¹⁹ An 8% v 0% anastomotic leak rate was reported for the preoperative chemo-radiation therapy arm compared to the surgery alone arm. A similar randomised trial by Urba et al, using a preoperative chemo-radiation therapy dose of 45 Gy reported an anastomotic leak rate of 15% v 8% for the chemo-radiation therapy arm compared to surgery alone arm.¹⁶ Burmeister et al reported on a randomised control trial performed within Australia using a dose of 35 Gy with a 5% anastomotic leak rate for both the preoperative chemo-radiation therapy arms and surgery arms.²³ Further research is required to determine the optimum radiation dose, however use of higher doses of radiation therapy offers patients a potentially curative treatment if they are unable to proceed to surgery due to a reduction in physical fitness or technical feasibility (eg. radiologically occult inoperable non metastatic disease).

Selecting which patients require trimodality surgery over definitive chemo-radiation therapy alone is unclear. The majority of evidence for preoperative chemo-radiation therapy is based on trials comparing the outcomes to a surgery alone arm. In a recent randomised control trial (FFCD 9102) there was an indication that not every patient requires trimodality therapy over chemo-radiation therapy alone.²⁴ In this trial, 444 patients were treated with two cycles of 5-FU and cisplatin, with concurrent radiotherapy of 46 Gy over four and a half weeks or two 15 Gy courses delivered over five days starting at day one and day 22 with chemotherapy. Patients who responded to treatment were then randomly assigned to further surgical resection or radiotherapy of either another 20 Gy over two weeks or 15 Gy over one week. With 250 patients randomly assigned to treatment, the two year local control rate for the surgical arm was 66% and 57% for the chemo-radiation therapy alone arms and the two year survival was 34% and 40% respectively. Additionally, the three month mortality rates were 9.3% compared to 0.8%. This reached the trial's criteria that there was a less than 95% chance that the two year survival for the chemo-radiation therapy alone arm was 10% worse than the surgery alone arms. Similar results have been reported in another randomised control trial of 172 patients treated with three cycles of induction chemotherapy followed by chemo-radiation therapy alone (65 Gy) or chemo-radiation therapy (40 Gy) and surgery.²⁵ Freedom from local progression was similarly lower in the arm with surgery as compared to chemo-radiation therapy alone arm (64% v 41%, $p=0.003$). The overall survival at two years was better for the surgery alone arm (40% v 35% $p=0.007$), however no statistically significant benefit was reported for patients who were responding to chemotherapy (survival at three years of 58% v 55%). These trials indicate that it may be possible to select patients who will benefit from multimodality preoperative chemo-radiation therapy and surgery based on treatment response. Use of other imaging modalities such F-18 fludeoxyglucose (FDG) PET scans may provide a better assessment of cancer response to treatment and predict for better outcomes from chemo-radiation therapy alone. In a recently reported single institution study, patients treated with definitive chemo-radiation therapy (50.4 Gy) had a PET scan before and after chemo-radiation therapy and also before surgical resection performed in 54% of the patients.²⁶ Median survival for patients treated with chemo-radiation therapy and surgery was 23.1 months (significantly better than chemo-radiation therapy alone arm of 13.9 months, $p<0.01$). Although PET complete response (31% of patients) did not predict for a better outcome in patients receiving surgery, it did predict for the chemo-radiation therapy alone arm with a median survival of 38 months v 11 months ($P<0.01$). As an imaging modality, FDG PET is the most reliable predictor of pathologic response to treatment and determinant of prognosis.^{27,28} Further investigation of the role and utility of FDG PET as both a predictive and prognostic factor post treatment is being performed by Australian and international groups. This recent paper along with other reported studies provide an area of ongoing evolution towards optimising individualised treatment of patients with oesophageal cancer.

The growing literature on preoperative chemo-radiation therapy has resulted in a growing adoption of trimodality

treatment in oesophageal cancer throughout the world. Selection of patients appropriate to this treatment approach should be performed within a multidisciplinary setting to ensure adequate patient fitness, surgical operability and the appropriate sequencing and timing of treatment.

Post-operative radiation therapy

Adjuvant radiation therapy or chemo-radiation therapy have a role in the treatment of oesophageal cancers. A few randomised control trials have shown that radiation therapy can reduce the local recurrence risk of patients with operable oesophageal cancer, however this has not translated into a survival benefit.^{29,30} The main benefit is mostly limited to patients with positive margins, reducing the local recurrence rate from 35-46% for surgery alone to 10-20% with adjuvant radiotherapy doses of 45 to 55 Gy. For gastro-oesophageal junction cancers, the gastric adjuvant chemo-radiation therapy study published by MacDonald et al showed both a survival and local control benefit with the addition of chemo-radiation therapy.³¹ In this study, using adjuvant 5-FU-based chemo-radiation therapy to a dose of 45 Gy, approximately 20% of patients had adenocarcinomas involving the gastro-oesophageal junction. A 10% absolute benefit in overall survival and reduced local recurrence rate was reported at three years for the radiotherapy arm (50% v 41% and 19% v 29%, respectively). These results must be interpreted with caution and not extrapolated for all oesophageal adenocarcinomas due to the differences in prognosis and outcomes. Adjuvant chemo-radiation therapy treatment volumes are also typically large for the gastro-oesophageal junction tumours, as the oesophago-gastric anastomosis (commonly located in the mid to upper thorax) and the regional draining gastric lymph nodes need to be covered. Based on the current literature, gastro-oesophageal junction tumours can be treated with adjuvant 5-FU-based chemo-radiation therapy for stage IB or higher disease. Radiation therapy or chemo-radiation therapy can be used to improve local control for oesophageal cancers and the doses typically used are similar to definitive doses of chemo-radiation therapy therefore can be considered for patients with gross residual oesophageal cancer if the patient is appropriately fit for treatment and it is technically feasible to deliver the radiation therapy dose.

Conclusions and future directions

Improvements in understanding of the molecular changes of oesophageal cancer will eventually allow improvements in individualisation of treatment of operable oesophageal cancer. Currently, multiple treatment approaches are available for treating operable oesophageal cancer including surgery alone, preoperative chemotherapy or chemo-radiation therapy and definitive chemo-radiation therapy alone. The evidence is mounting that neoadjuvant therapies including chemo-radiation therapy can improve the cure rate for locally advanced operable oesophago-gastric cancers and should be considered in the current treatment paradigm of oesophago-gastric cancers. Use of molecular targeted agents may improve outcomes of patients with operable oesophageal cancer and the integration of these is currently being investigated. The current Australian led clinical trials for operable oesophageal cancers include a

randomised trial comparing three cycles of preoperative epirubicin, cisplatin and 5-FU alone, or two cycles of the same chemotherapy in addition to preoperative 5-FU based chemo-radiation therapy for operable gastric and gastro-oesophageal junction cancers (TOPGEAR), and a randomised phase II trial of preoperative cisplatin, 5-FU with or without docetaxel and/or radiotherapy depending on early FDG PET response to chemotherapy for operable oesophageal or gastro-oesophageal junction cancers. These studies will help to clarify key areas of controversy in the management of gastro-oesophageal cancers.

The current approach to treating oesophageal cancer is predominantly based on the technical suitability of a patient to surgery, chemo-radiation therapy or preoperative chemo-radiation therapy. This requires a multidisciplinary assessment and discussion on the suitability of each approach. Typically oesophageal cancer in the lower third is technically easier to resect than those in the upper two thirds of the oesophagus and may determine the suitability for surgical resection. The use of functional imaging (eg. pre and post treatment FDG PET) may facilitate the determination of the optimal treatment strategy for patients with operable oesophago-gastric cancers.

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