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**Role of radiotherapy in the pre-operative management of carcinoma of the esophagus**

Burmeister BH. Neoadjuvant radiotherapy for esophageal cancer

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**Abstract**

The use of radiotherapy in the management of carcinoma of the esophagus and gastro-esophageal junction has undergone much evolution over the past 2 decades. Advances to define its role have been slow with meta-analyses often providing the most useful data. In spite of this many institutions around the world are divided about the role of radiotherapy in this disease and attribute different roles to radiotherapy based on clinical stage, tumor site and histology. The purpose of this review is to try to define the role of radiotherapy given our current knowledge base and to review which current or future trials may fills the gaps of knowledge that we currently have. It will also highlight the difficulties in making firm recommendations about the use of radiotherapy especially in a time when technology and treatments are rapidly evolving.

**Key words:** Esophageal cancer; Preoperative therapy; Neoadjuvant therapy; Chemoradiotherapy; Surgery

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**Core tip:** This review describes the history and development of radiotherapy in the pre-operative setting for resectable esophageal cancer. In particular it focuses on data from multicentre phase II and phase III trials as well as meta-analyses from across the world. The review concludes with a discussion about the role of new radiation technologies in the management of esophageal cancer.

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**INTRODUCTION**

The issue of improving loco-regional control and possibly survival for resectable esophageal cancer has been a subject of interest for about the last 3 decades. Prior to 1980 radiotherapy was used mostly as sole modality for therapy when patients were not suitable for surgery. Response rates and survival however were low and it was only when chemotherapy was added to radiotherapy that response rates improved and long term remissions from the disease were noted. At the time, squamous cell carcinoma (SCC) was the predominant cell type and being a relatively responsive disease, most early clinical trials involving pre-operative therapy were confined to that histology. It was only in the late 1990s that some investigators began to include adenocarcinoma (AC) in neoadjuvant clinical trials on the basis that if surgery was to be the major treatment modality, histological subtype might not play a major role in outcomes. In this review I trace the progress of the early trials involving SCC only, the combined histology trials and finally some of the meta-analyses, most of which have included both histological subtypes. The dilemma however is far from resolved with the issue of whether radiotherapy adds real benefit to systemic therapy in terms of survival and loco-regional control yet to be determined in a randomized trial.

**PRE-OPERATIVE RADIATION THERAPY**

Following the suggestion that radiotherapy may lead to a complete pathological response (pCR) in some patients prior to surgery in esophageal cancer, some investigators did report non-randomized retrospective comparisons of surgery alone versus pre-operative radiotherapy followed by surgery. Radiation doses ranged from 20-60 Gy and there were some reports of a survival improvement in those treated with both radiotherapy and surgery, although these studies were non-randomized and clearly a possibility of better performance status patients having combined modality therapy existed. It was not long however before randomized trials were devised to assess outcomes following pre-operative radiotherapy. Between 1981 and 1992 five randomized trials were reported[1-5]. All of these involved SCC and radiation doses varied from 20-40 Gy. Survival outcomes were inconsistent with 3 trials reporting improved survival with pre-operative radiotherapy[2,3,5] and 2 had better survival in the surgery alone arm[1,4]. None of these results however reached statistical significance. Nevertheless an average of 15% of patients did achieve a pCR and local failure rates ranged from 20%-58%. Since that time radiotherapy as a single modality is seldom used as a sole modality in the pre-operative setting.

**PRE-OPERATIVE CHEMORADIOTHERAPY**

The use of pre-operative chemoradiotherapy in esophageal cancer was first used in 2 phase II studies based in the United States[6,7]. The Southwestern Oncology Group (SWOG) trial accrued 113 patients treated with pre-operative chemoradiotherapy using concurrent cisplatin, fluorouracil and 30 Gy. Median survival was 12 mo and 3 year survival 16%[7]. The RTOG study had even poorer survival[6]. Several other phase II trials incorporating tri-modality therapy have been done, including some incorporating newer chemotherapy agents including paclitaxel, carboplatin and oxaliplatin. Most show similar median survival times of 20%-58% although the selection criteria for these studies vary and may well affect the different outcomes.

There have been numerous randomized trials comparing surgery alone with pre-operative chemoradiotherapy followed by surgery[8-14]. The earlier studies only involved patients with SCC but more recent ones included both histologies. The first to report a positive outcome in favor of tri-modality therapy was that by Walsh *et al*[12] who only reported the outcomes of a subset of AC patients despite the fact that both subtypes were included in the trial[12]. Although the outcome was significantly beneficial in terms of survival for those receiving chemoradiotherapy, the trial has been criticized as the workup imaging did not include CT scanning of the chest and abdomen and the outcomes of the surgery alone arm were exceptionally poor. More recently the trials by Tepper[15] and the CROSS study by van Hagen[16] have clearly shown benefits in survival and these have both been based on high tumor response rates including pCR rates in the experimental arm. Some of the other chemoradiotherapy trials have shown benefits for subgroups. The Australian trial by Burmeister showed a benefit for patients with SCC but not AC and then because AC constituted the majority of patients recruited to the trial, there was no overall survival benefit[14]. In the trial by Urba, the benefit was seen in overall survival at 3 years but the difference did not reach statistical significance[13]. Other trials in this area have been negative in terms of survival but have also been criticized because of having low doses of radiotherapy and split courses of treatment.

**OUTCOMES OF META-ANALYSES**

Meta-analyses (MAs) are frequently used to reach conclusions about absolute trial endpoint such as survival when individual trials don’t have enough numbers to provide statistically significant outcomes. The problem is that when trials are included in MAs the sample populations may be different with different eligibility criteria, requirements for clinical staging and in esophageal cancer, different histological subtypes. Requirements for clinical staging may be evolutionary in that earlier trial investigators may not have had access to more contemporary forms of imaging such as computerised tomography (CT) or positron emission tomography (PET). This means that some of the earlier trials may have included patients with more advanced disease that would be excluded by more modern forms of imaging. Another issue with MAs is that they often fail to address secondary endpoints such as loco-regional control, pCR rates, resectability rates, toxicity and quality of life, unless all the trials included these endpoints and the same methodology in assessing them was used.

***Radiotherapy plus surgery versus surgery alone***

For patients having pre-operative radiotherapy alone, there is only one MA which has been published on multiple occasions as a Cochrane review[17]. This review involved all 5 randomized trials comparing surgery alone with pre-operative radiotherapy followed by surgery. The dominant histology was SCC although some trials did include AC. The outcomes was an improvement in survival in those patients receiving combined therapy although this did not reach statistical significance (*P* = 0.06).

***Chemoradiotherapy plus surgery versus surgery alone***

There are multiple MAs involving a comparison of surgery alone with pre-operative chemoradiotherapy[18-23]. These have evolved with the completed trials. The first of these to be published was by Urschel in 2003 and involved more than 1000 patients from 9 randomized trials[18]. They concluded there was a benefit for pre-operative chemoradiotherapy in terms of survival at 3 years. The most widely quoted meta-analysis was published by Gebski in 2007 combining results of 10 trials and more than 1200 patients[22]. They found a significant benefit in terms of all-cause mortality for those patients receiving pre-operative chemoradiotherapy with a hazard ratio of 0.81 (95%CI: 0.70-0.93; *P* = 0.002). Three years later the same group updated their results with outcomes from 12 trials and 1854 patients[23]. The hazard ratio for all-cause mortality with patients receiving pre-operative chemoradiotherapy was 0.78 (95%CI: 0.70-0.88), *P* < 0.0001), indicating a more definite result in favor of neoadjuvant therapy.

***Chemoradiotherapy plus surgery versus chemotherapy plus surgery***

The meta-analysis by Sjoquist also included a subgroup review of comparisons of pre-operative chemotherapy versus pre-operative chemoradiotherapy[23]. Only 2 trials were able to be included. Both included only patients with AC and both were underpowered. The first one published by Stahl included junctional tumours and a long extended course of neoadjuvant chemotherapy[24]. The second by Burmeister had a much shorter chemotherapy regimen and included only esophageal cancer patients[25]. It did suggest that trimodality therapy did improve resectability rates. Neither trial showed a survival benefit for trimodality over bimodality therapy, both being concluded prematurely due to poor accrual. The hazard ratio for these 2 trials combined was 0.77 (95%CI: 0.53-1.12; *P* = 0.17) in favor of neoadjuvant chemoradiotherapy. This however is clearly not significant and more trials comparing these 2 approaches are required and are currently being conducted.

***Individual patient data meta-analysis***

In 2013 Ronellenfitsch and colleagues published a more detailed MA involving individual patient data (IPD)[26]. This is a more sophisticated form of MA in that it enables one to look at subgroups and secondary outcomes in more detail. Unfortunately this MA also did not include the CROSS trial, and some trial chairs refused to provide IPD. Not only did this MA confirm the survival benefit seen in patients receiving neoadjuvant chemotherapy and chemoradiotherapy, but it also detected an improved benefit for junctional tumours. Improved benefits were also noted for other subgroups, such as ECOG performance status 0, male gender and age < 65 years. They were also able to look at disease-free survival in some trials which mirrored outcomes in overall survival, although not reaching statistical significance. They also found no difference in post-operative morbidity or mortality. They were however unable to further define the role of radiotherapy in the pre-operative management of esophageal cancer using the IPD that they managed to procure.

**NEW RADIOTHERAPY TECHNOLOGIES**

Radiotherapy technology has been rapidly evolving over the past decade with most tumors and sites now being bale to be treated with highly conformal therapies including intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT). These new technologies have enabled the oncologist to deliver high doses of radiation with more precision to the tumor and at the same time spare surrounding tissues and organs which has dramatically reduced morbidity. In esophageal cancer the uptake of these modalities has been slow but in currently imbedded in most new protocols involving definitive treatment. It is only a matter of time until they are routinely used in the neoadjuvant setting where the big gain will be in offsetting radiation related surgical morbidity with high doses. It also may enable one to delay surgery which is currently conducted 4-8 wk post radiotherapy to 10-12 wk post radiotherapy. This in turn may make it possible to avoid surgery in some patients where a complete endoscopic and PET related response has been achieved. This concept of “surgery as needed” is increasingly being adopted at other sites where neoadjuvant chemoradiotherapy is used and has the potential to not only reduce health costs but improve quality of life for patients during their cancer journey.

**DISCUSSION**

One of the big issues around assessing the value of the local treatment modality is deciding on the magnitude of its benefit if there is indeed one. Local treatment modalities such as surgery and radiotherapy aim primarily to control tumors at the primary site and/or regional lymph nodes in order to reduce or eliminate the problems associated with uncontrolled tumor and the effects it may have function, cosmesis, and control of local symptoms. In the esophagus elimination of dysphagia is a principle aim of local treatment with surgery being able to do this effectively with all small tumors and radiotherapy with some small tumors especially SCC. Better control rates are theoretically obtained with these 2 modalities are combined in more advanced tumors. Radiotherapy given in the pre-operative setting has the advantage of being able to downstage tumours and make resections easier with less chance of having involved margins.

However in order to have an impact on survival, comparisons of different local treatment modalities require large numbers of patients because improvements in local control will only result in a survival benefit in a small proportion of those who experience a local control benefit. This means that most published randomized clinical trials comparing local modalities have not shown a survival benefit but rather one in terms of local control and improved resectability where surgery has been involved.

On the other hand trials that have added a systemic therapy such as chemotherapy to one arm of the trial could be expected to possibly confer a survival benefit. This is on the basis of many patients already having subclinical metastatic disease that a systemic agent may be able to control or delay converting in to overt metastases. In addition the chemotherapy agents used in esophageal cancer have useful radio-sensitizing properties which may enhance the effects of radiotherapy and further improve local outcomes. It is however unknown whether an exceptionally good local outcome such as pCR at time of surgery is always associated with prolonged survival although many studies suggest that it does.

Many of the randomized trials involving chemotherapy have shown a survival benefit in their own right. Some such as the Walsh trial12 have been interpreting as having a suboptimal result in the control arm whilst other more recent trials such as the CROSS trial clearly show a survival benefit for combined modality therapy and an improvement in local outcomes as well[16]. So in summary we still need to decide which patients require radiotherapy in addition to surgery plus platinum-based chemotherapy. The MAs and some trials suggest the all SCC patients may benefit. However the case in AC is far less clear, with possible more advanced tumors, those with ill defined resection margins on CT and those with nodal disease more likely to benefit in terms of local control. This hypothesis however is far from confirmed.

So what is clear right now is that although the most recent complete MA by Sjoquist[23] clearly demonstrates an improved survival advantage for neoadjuvant chemoradiotherapy when compared to neoadjuvant chemotherapy, this approach may not be required in all patients. More trials comparing these 2 modalities are being done but will take several years to analyze and may not have enough patients to give answer to all the endpoints apart from survival. Issues such as local control, respectability, toxicity and cost all are relevant in the current era. By doing more MAs involving IPD one has the potential to look at subgroups and secondary endpoints more rigorously and hopeful identify optimum therapies for patients.

**CONCLUSION**

At the time of writing this review there remains controversy on the role of radiotherapy as part of a combined package with chemotherapy as a neoadjuvant therapy for operable esophageal cancer. Completion of the ongoing clinical trials investigating this role and sharing of the data as part of further MAs will add to our knowledge base in the management of esophageal cancer.

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