Radiotherapy and Oncology 113 (2014) 166–174

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic Review

# A qualitative synthesis of the evidence behind elective lymph node irradiation in oesophageal cancer

Lien Van De Voorde [a,*], Ruben T.H.M. Larue [a], Madelon Pijls [b], Jeroen Buijsen [a], Esther G.C. Troost [a], Maaike Berbée [a], Meindert Sosef [c], Wouter van Elmpt [a], Marie-Céline Schraepen [c], Ben Vanneste [a], Michel Oellers [a], Philippe Lambin [a]

[a] Department of Radiation Oncology (MAASTRO), Maastricht UMC+; [b] Health Insurance Company, CZ, Tilburg; and [c] Department of Surgery, Atrium Medical Center, Heerlen, The Netherlands

ARTICLE INFO

*Article history:*
Received 3 September 2014
Received in revised form 10 October 2014
Accepted 9 November 2014
Available online 25 November 2014

*Keywords:*
Oesophageal cancer
Radiotherapy
Lymph node
Surgery
Review
Elective

ABSTRACT

*Background and purpose:* Oesophageal cancer is the sixth leading cause of cancer death worldwide and radiotherapy plays a prominent role in its treatment. The presence of lymph node (LN) metastasis has been demonstrated to be one of the most significant prognostic factors related to oesophageal cancer. The use of elective lymph node irradiation (ENI) is still a topic of persistent controversy. The conservative school is to irradiate positive lymph nodes only; the other school is to prophylactically irradiate the regional lymph node area according to different tumour sites. This review investigated the justification for including ENI in the treatment of patients with oesophageal cancer. *Material and methods:* We performed a systematic literature search to find surgical data about lymph node distribution depending on different tumour subgroups: early, cervical, thoracic and gastroesophageal junction cancer. Furthermore, we performed a qualitative assessment of recurrence patterns in patients treated with or without ENI to derive estimates of the potential area at risk for lymph node harvest. *Results:* We identified and reviewed 49 studies: 10 in early, 8 in cervical, 10 in thoracic and the remaining 21 in gastroesophageal junction cancer. In general, these studies were conclusive in incidence and location of pathologic lymph nodes for different subgroups. Data for lymph node recurrence patterns are scarce and contributed little to our review. *Conclusions:* This review resulted in five recommendations for radiation oncologists in daily practice. We used the available evidence about metastatic lymph node distribution to develop a careful reasonable radiation protocol for the corresponding tumour subgroups.


Oesophageal cancer is the sixth leading cause of cancer death worldwide and radiotherapy plays a prominent role in its treatment. Adenocarcinoma of the oesophagogastric junction (AEG) is increasingly common in the Western world and its prevalence now equals or surpasses that of squamous cell carcinoma (SCC) [1,2]. Reports have shown better [3–5], similar [6,7] or inferior long-term survival [8–10] rates for patients with SCC compared to those with AEG.

There is evidence that complete response to neoadjuvant chemoradiotherapy (nCRT) is associated with significant improved outcome with five-year overall survival rates up to 55% [11,12]. Regardless of the histological subtype, oesophageal cancer (EC) is notorious for its submucosal "skip" invasion because of the extensive and longitudinal interconnecting system of lymphatics in the oesophagus [13–15]. Although Stahl's study [16] was closed early and statistical significance was not achieved, it found that patients treated with chemoradiotherapy (CRT) had a significant higher probability of showing tumour-free lymph nodes (64.4% vs. 37.7%) at resection than patients treated with chemotherapy alone.

A recent study by Muijs [17] demonstrated that microscopic tumour outside the clinical target volume (CTV) is associated with markedly worse overall survival after nCRT. There is no doubt that effort should be made to optimise preoperative treatment schedules in order to convert patients to the group with complete histopathological response [18,19]. One rationale for using CRT before surgery is the elimination of micrometastases (MM). Micrometastases and "isolated tumour cells" are not detected by routine histological examination and definitions may vary in the literature [20]. Micrometastases can be detected in up to 50% of radical resected oesophageal tumours without overt nodal involvement [21]. A

* Corresponding author at: MAASTRO Clinic, Doctor Tanslaan 12, 6229 ET Maastricht, The Netherlands.
*E-mail address:* Lien.vandevoorde@maastro.nl (L. Van De Voorde).

http://dx.doi.org/10.1016/j.radonc.2014.11.010
0167-8140/

growing body of evidence suggests that immunohistochemically detected micrometastatic deposits in oesophageal cancer are associated with reduced survival [22,23] and increased risk of disease recurrence [21,24], even in patients with pathologic node-negative disease. The neoadjuvant approach is able to significantly reduce nodal micrometastasis (even up to 30%) regardless of SCC or adenocarcinoma [25]. The clinical relevance of these MM may depend on environmental, interpersonal or intermodal variation, but this remains difficult to predict. Although a host's immune system may be able to remove a single tumour cell, it may be reasonable to advocate inclusion of the elective node region to eradicate or diminish residual cells with metastatic potential [22,26]. This underlines the importance of accurate tumour delineation and the need to justify elective lymph node irradiation (ENI).

There are still concerns about the adverse perioperative effects of ENI and its long-term toxicity because of the potential unnecessarily large treatment volumes [27,28]. Most studies have found little association between the risk of postoperative mortality (in-hospital or 30-day postoperative death) and the neoadjuvant interventions, even when the elective node region is included [29–31]. However, a recent study showed that oesophagogastric anastomosis placed within the preoperative radiation field (gastric margin) was a very strong predictor for anastomotic leaks in oesophageal cancer patients treated with trimodality therapy. These finding emphasise the need for critical evaluation of the radiotherapy field [32,33]. The use of intensity-modulated radiotherapy can reduce the associated burden on the organs at risk, but it also leads to a reduction of the historical incidental irradiation of nearby high-risk nodal regions [34]. Besides more sophisticated radiation techniques, also nodal staging became more accurate in the past decades due to improved imaging modalities. However, the sensitivity of positron emission tomography (PET), computed tomography (CT), endoscopic ultrasound (EUS) and more recently even magnetic resonance imaging (MRI) remains poor. The additional value of EUS depends strongly on the distance from the probe to the lymph node which can be problematic in adenocarcinoma. In up to 30% of oesophageal cancers the probe is not able to pass the tumour. We expect promising results from MRI but overcoming image artefacts due to respiratory and cardiac motion will be challenging [35]. Metastatic lymph nodes are often only slightly larger in than non-involved nodes (6.7 mm vs. 5 mm) [36]. Correct assessment of metastatic lymph nodes is important because complete local response may be accompanied by residual locoregional metastatic lymph nodes in up to 10% of patients with pathological complete response (pCR) [37]. Detailed knowledge of LN patterns from LN dissections as provided in this overview manuscript can contribute to correct radiation target volume delineation.

In this review, we will give insight into the frequency of involved nodes in several surgical specimens and define the areas at greatest risk for disease spread for different tumour groups: early, cervical, thoracic and gastroesophageal junction tumours. Since the success of the local effect of radiotherapy has to be judged foremost on locoregional tumour control, we also evaluated the pattern of recurrence to clarify the rationale and benefits in terms of outcome for ENI.

## Methods

We searched the Medline/PubMed database using the following primary keywords: 'lymph node', 'elective or neoadjuvant therapy', 'oesophagus or oesophageal or esophageal cancer or carcinoma', 'surgery or operation or oesophagectomy', 'radiotherapy or irradiation'. Only English-language articles published between January 1992 and September 2014 were included. Studies that included metastatic disease were not included. We reviewed the reference lists of all the identified trials, review articles and meeting abstracts. We also performed a manual search of relevant studies to complete this review. If trial results were subsequently updated, we used the information from the more recent publication. Literature data that were already addressed in meta-analyses were not added separately to our analysis.

Two reviewers independently extracted data and transferred it into a table documenting the number of patients in the trial, the proportion with squamous cell and adenocarcinoma, radiation details (dose, field, fractionation, duration), chemotherapy details, the number of patients undergoing surgery and lymph nodes retrieved, the topography of the lymph nodes, overall survival (median, two, three and five years), relapse and regional recurrence. For the purpose of this overview, we excluded small trials that treated fewer than 15 patients. Several lymph node classifications and nomenclatures have been used to facilitate the identification of lymph nodes, e.g., RTOG lymph node map [38], the classification of Akiyama [39] and Japanese Society for Oesophageal Diseases (Supplementary Appendix).

## Results

The original search retrieved 112 hits. Of those, 42 papers were identified as potentially relevant. Duplicates and clearly irrelevant references were excluded. An additional manual search found 17 more papers, resulting in a total of 59 references for inclusion in this review. They are categorised as follows: early ($n = 10$), cervical ($n = 8$), thoracic ($n = 10$) and gastroesophageal junction tumour ($n = 21$). We also included 10 articles that described recurrence patterns in patients with oesophageal cancer who were treated with CRT with ($n = 4$) or without ENI ($n = 6$) to complete the review.

### *Early oesophageal cancer*

Early oesophageal cancers are classified into the following subcategories: Tis (high-grade dysplasia), T1a or T1b. Endoscopic mucosal resection (EMR) has been recognised as a safe and feasible procedure for treating T1a tumours. Before extending indications of this endoscopic treatment, a thorough search in literature with prediction of lymph node invasion is obligate [40]. Once submucosal invasion is present, there is a substantial risk of lymph node metastasis (LNM): it ranges from 10% to 30% when infiltrating the upper and middle submucosal layer, but up to 60% once it reaches the third layer [41–50]. Lymphovascular invasion (LVI), poor differentiation, non-flat shape and tumour length are associated with a higher risk for lymph node metastasis [42,49].

In 2000, the Japanese Society for Radiation Oncology (JASTRO) published a consensus guideline for standard radiotherapy and chemoradiotherapy, describing it as a safe and effective method for treating superficial oesophageal cancer [51]. They found three-year survival rates of mucosal cancer and submucosal cancer patients that were 90% and 70%, respectively. These survival rates are comparable with those of patients treated with surgery [52,53]. An ongoing randomised trial is comparing definitive chemoradiotherapy with surgery for patients with stage I disease who are not candidates for endoscopic resection (JCOG 0502).

The surgical data in Table 1 show that lymph node metastases are predominantly located near the primary tumour. Skipping the adjacent lymph node stations is rare, especially in early oesophageal adenocarcinoma [54]. Studies that included ENI support this approach and assert that it prevented any regional recurrence [53]. Studies in which no ENI was performed reported an incidence of regional failure up to 15%. In general, no significant improvement of overall survival was reported for using ENI