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Review

Lymph node yield after rectal resection in patients treated with neoadjuvant radiation for rectal cancer: A systematic review and meta-analysis

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Abstract ***Background:*** The lymph node status represents a major prognostic factor in colorectal cancer. However, it was demonstrated that neoadjuvant chemoradiotherapy (CRT) decreases the numbers of lymph nodes in the specimen. Several studies describe less than 12 lymph nodes in the resected specimen of rectal cancer patients after neoadjuvant radiation. This meta-analysis quantifies the influence of neoadjuvant CRT or radiotherapy (RT) only on the lymph node yield in rectal cancer patients.

Methods: We performed a systematic review and searched PubMed, EMBASE and the Cochrane Library without any language restriction from 1st of January 1980 until 31st March 2015. Two reviewers examined all publications independently and extracted the relevant data if the study assessed lymph node counts or positive lymph node yields of patients who received neoadjuvant treatment compared with patients who did not receive neoadjuvant treatment. Meta-analyses were conducted to quantify the mean difference in lymph node yield.

Results: A total of 34 articles (including 37 datasets) were included in the meta-analyses. Neoadjuvant CRT resulted in a mean reduction of 3.9 lymph nodes (95% confidence interval [CI] 3.7–4.1) and an average reduction in harvested positive lymph nodes of 0.7 (95% CI 0.2–1.2) compared with patients who received no neoadjuvant therapy. Individuals who received neoadjuvant RT had, in average, 2.1 lymph node less (95% CI 1.7–2.5) resected compared with their counterparts who received no neoadjuvant treatment.

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Conclusions: Neoadjuvant CRT or RT only in rectal cancer patients leads to a decrease in lymph node harvest of approximately four and two lymph nodes, respectively. We therefore stress the importance of intensifying all efforts from involved subspecialities (i.e. surgeons and pathologists) to reach the benchmark harvest of 12 resected lymph nodes according to current guidelines.

1. Introduction

With an incidence of 1.4 million cases in 2012, colorectal cancer represents one of the most common cancers worldwide [1], second most diagnosed in females and third in males. Despite a decrease over the last centuries, most likely due to enhanced screening, reduced prevalence of risk factors and/or improved treatment [2–4], the mortality rate with 693,000 deaths worldwide in 2012 remained high [1]. The global burden was estimated to be as high as 14.4 disability-adjusted life years [5], and the lifetime probability of developing invasive colorectal cancer in the United States was assessed to be between 4.4% and 4.7% [4].

In rectal cancer, neoadjuvant chemoradiotherapy (CRT) followed by curative surgery including total mesorectal excision (TME) has become the standard of care for the International Union against Cancer stage II or III [6]. This way a systematic lymphadenectomy can be performed, resulting in the lymph node status (pN) which is defined as the number of tumour-infiltrated lymph nodes [7]. The pN represents a major prognostic factor and the total number of resected lymph nodes correlates significantly with the relapse of disease and overall survival [8–12]. Besides showing an adequate oncologic surgery [13], it additionally represents a quality parameter and plays an essential role in management decisions concerning adjuvant treatment protocols [14]. However, the prognostic importance of the number of metastatic lymph nodes in patients who have only a small number of retrieved lymph nodes compared with patients who have several lymph nodes retrieved after radio (chemo)therapy remains not entirely clear.

The current guidelines from the American Joint Committee on Cancer and the International Union against Cancer defined a minimum of 12 lymph nodes to be examined to reach an appropriate pN staging to avoid understaging [7,15,16]. While the extent of tumour resection in colorectal cancer is well defined and should not differ depending on the application of a neoadjuvant radio(chemo)therapy [14], the numbers of retrieved lymph nodes vary between reported patient series. Chou *et al.* [17] even demonstrated that only 49% of patients undergoing surgery for colorectal cancer met the suggested standards concerning lymph node yield.

While neoadjuvant CRT and radiotherapy (RT) only has been shown to induce shrinkage of the tumour and improved local control [18–20], several studies demonstrated a decrease of the number of lymph nodes examined in these pretreated mesorectal specimens [21–26].

Given the importance of pNand its implication on outcome, we performed the first series of meta-analyses to quantify the influence of preoperative CRT and RT in rectal cancer patients on number of retrieved lymph nodes in the specimens.

2. Methods

2.1. Search strategy and inclusion criteria

For this systematic review, we adhered to the Meta-analysis of Observational Studies guidelines [27] and the Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement [28] (appendix). The study protocol for this systematic review and meta-analysis can be reviewed in Appendix. In brief, PubMed, EMBASE and the Cochrane Library were systematically searched for relevant studies from 1st January 1980 until 31st March 2015 without language restrictions. We used the MeSH terms and keywords 'lymph node', and 'lymph node ratio'. These terms were combined with 'colorectal cancer', 'rectal cancer', 'rectal carcinoma' and 'rectal resection'. This search was then again combined with the MeSH terms and keywords 'preoperative therapy', 'preoperative radiation', 'preoperative chemoradiotherapy', 'preoperative radiotherapy', 'preoperative radiochemotherapy', 'neoadjuvant therapy', 'neoadjuvant radiation', 'neoadjuvant chemoradiotherapy', 'neoadjuvant radiotherapy' and 'neoadjuvant radiochemotherapy'. Regardless of the study type, publications were eligible for inclusion if they compared quantitative data on lymph node harvest in resected specimen of human rectal cancer patients between individuals who received preoperative RT only or CRT versus patients who received no neoadjuvant therapy.

In the first step, all identified titles and abstracts were examined by two independent reviewers (RM and BS). In the second step, the same two reviewers independently examined the full text of potentially relevant articles. The eligibility of the studies was assessed using the study protocol (Appendix). In case of disagreement, a third reviewer (RR) was consulted and the respective article was discussed until a consensus was reached.