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Systematic or Meta-analysis Studies

Postoperative radiotherapy for lung cancer: Is it worth the controversy?

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ABSTRACT

Introduction: The role of postoperative radiation therapy (PORT) in patients with completely resected non-small cell lung cancer (NSCLC) with pathologically involved mediastinal lymph nodes (N2) remains unclear. Despite a reduction of local recurrence (LR), its effect on overall survival (OS) remains unproven. Therefore we conducted a review of the current literature.

Methods: To investigate the benefit and safety of modern PORT, we identified published phase III trials for PORT. We investigated modern PORT in low-risk (ypN0/1 and R0) and high-risk (ypN2 and/or R1/2) patients with stage III-N2 NSCLC treated with induction chemotherapy and resection.

Results: Seventeen phase III trials using PORT were selected. Of all PORT N2 studies, 4 were eligible for evaluation of LR, all in high-risk patients only. In these high-risk patients receiving PORT, the mean LR rate at 5 years was 20.9% (95% CI 16–24). Two trials were suitable to assess LR rates after chemotherapy and surgery without PORT. In these low-risk patients, the mean 5-year LR was 33.1% (95% CI 27–39). No significant difference in non-cancer deaths between PORT vs. non-PORT patients was observed in N2 NSCLC.

Conclusion: PORT is worth the controversy because data illustrate that PORT may increase the OS. However, prospective randomized trials are needed to verify this.

Introduction

Lung cancer is one of the main causes of cancer deaths [1]. Non-small-cell lung cancer (NSCLC) accounts for about 80% of all cases, and one-third of these patients are diagnosed with stage III disease.

Multimodality therapy is the standard of care for patients with stage III NSCLC, but there are several therapeutic options. Most patients with stage III-N2 NSCLC receive concurrent or sequential chemoradiotherapy, depending on their vital status. Alternatively, a surgical multimodality treatment can be offered for patients with resectable stage III NSCLC [2,3]. Three phase III studies have addressed the role of surgery in stage III-N2 NSCLC [2,4,5]. In the ESPATUE trial, after cisplatin-based induction chemotherapy followed by concurrent chemoradiotherapy (45 Gy), resectable patients were randomized between surgery and a chemoradiotherapy boost (20–26 Gy) [4]. No differences in overall survival (OS) or progression-free survival (PFS) were observed. The Swiss Group for Clinical Cancer Research randomly assigned patients with proven IIIA-N2 to induction chemotherapy with three cycles of cisplatin/docetaxel followed by surgery, versus induction sequential chemoradiotherapy consisting of three cycles of cisplatin/docetaxel and 44 Gy of radiation, followed by surgery. No significant benefit in OS or event-free-survival was reported [2]. The third trial compared concurrent induction chemoradiation (cisplatin-etoposide, 45 Gy) followed by surgery to definitive concurrent chemoradiation (61 Gy) [5]. Again, no differences in OS were observed, although the PFS was longer in the surgical arm. However, the general outcome remains poor in all treatment groups, with a 5-year OS between 25% and 35% and high rates of local and distant failures [2,4,6].

The beneficial effect of adjuvant or induction chemotherapy has been proven in many phase III studies. An update of the 1995 MRC meta-analysis [7] in 2010 [8] including a total of 8447 patients in

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34 trials, showed an absolute difference in the 5-year OS rate of 4% at 5 years (64% versus 60%; HR = 0.86) in favor of chemotherapy. The beneficial effect of adjuvant chemotherapy was also observed in the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis, which pooled individual patient data from 5 trials, with an absolute OS increase of 5.4% at 5 years in patients with completely resected NSCLC (HR = 0.89) [9,10].

In contrast with the consensus about (neo)-adjuvant chemotherapy, the role of postoperative radiotherapy (PORT) remains controversial. PORT could be a logical choice because, even after downstaging with chemotherapy followed by surgery, local recurrence rates (LR) remain high. The first site of recurrence is local in about 30% of the patients and the cumulative rate of LR is 50–60% [2,6,11–13]. PORT may decrease LR and improve OS, when using modern (linac-based) treatment techniques. In a recent meta-analysis, based on published randomized phase III trials, PORT significantly decreased LR when administered with linear accelerators (RR 0.31, 95% CI 0.12–0.79, p = 0.01). Based on these results, we hypothesized that PORT could decrease LR by 20% (from 30% to 10%) when delivered with modern techniques (Fig. 1). This could theoretically lead to a 13% absolute increase in OS for stage III-N2 NSCLC patients [14,15]. PORT thus consistently reduces LR rates by 20% (absolute gain), but its effect on overall survival remains unproven.

To administer PORT or not remains controversial. In this review we will evaluate the data of PORT on LR and OS in order to answer the question if the discussion of PORT is worth the controversy, i.e. should the subject be closed or is continued research worthwhile?

Materials and methods

PORT in phase III trials

A comprehensive review of the literature was performed on MEDLINE to identify publications relating to the use of postoperative radiotherapy in NSCLC. Following key-words were used: 'non-small cell lung cancer', 'postoperative radiotherapy', 'radiation therapy', 'adjuvant treatment', 'toxicity', 'local recurrence and 'overall survival'. Both prospective and retrospective trials were eligible. Only studies published in English were included with inclusion period between 1960 and March 2016. Studies were excluded when they did not include radiotherapy or non-small cell lung cancer (NSCLC) patients, when they studied other radiation qualities than photons (e.g. protons) or when no surgery was performed. Titles and abstracts were screened by the main author; papers that were selected were verified by the co-authors.

We used I^2 statistics, which estimate the proportion of variability of the results related to heterogeneity rather than to sampling error. An I^2 of 25% or less corresponds to a low heterogeneity [16].

LR after resection and induction chemotherapy +/− PORT

We performed another MEDLINE search to identify published data investigating current LR rates in stage III-N2 NSCLC patients in particular, treated with a surgical resection and (neo)-adjuvant chemotherapy without PORT.

Secondly, we selected studies from the above collected PORT data to obtain information about LR rates in stage III-N2 NSCLC patients treated with a surgical resection and (neo)-adjuvant chemotherapy. Trials were eligible for inclusion if the study population was at least 40 patients with at least 2 years of follow-up and if patients received cisplatin-based chemotherapy. Only recent studies from the year 2000 onwards were selected as a surrogate for modern staging and treatment techniques.

From the collected data above, we calculated the mean of the first relapse rates. Upper and lower limits of the 95% confidence intervals were calculated. We divided the studies in two different patient groups: high-risk patients having no mediastinal downstaging after chemotherapy (ypN2) and/or an incomplete resection after surgery (R1/2), and low-risk patients with mediastinal

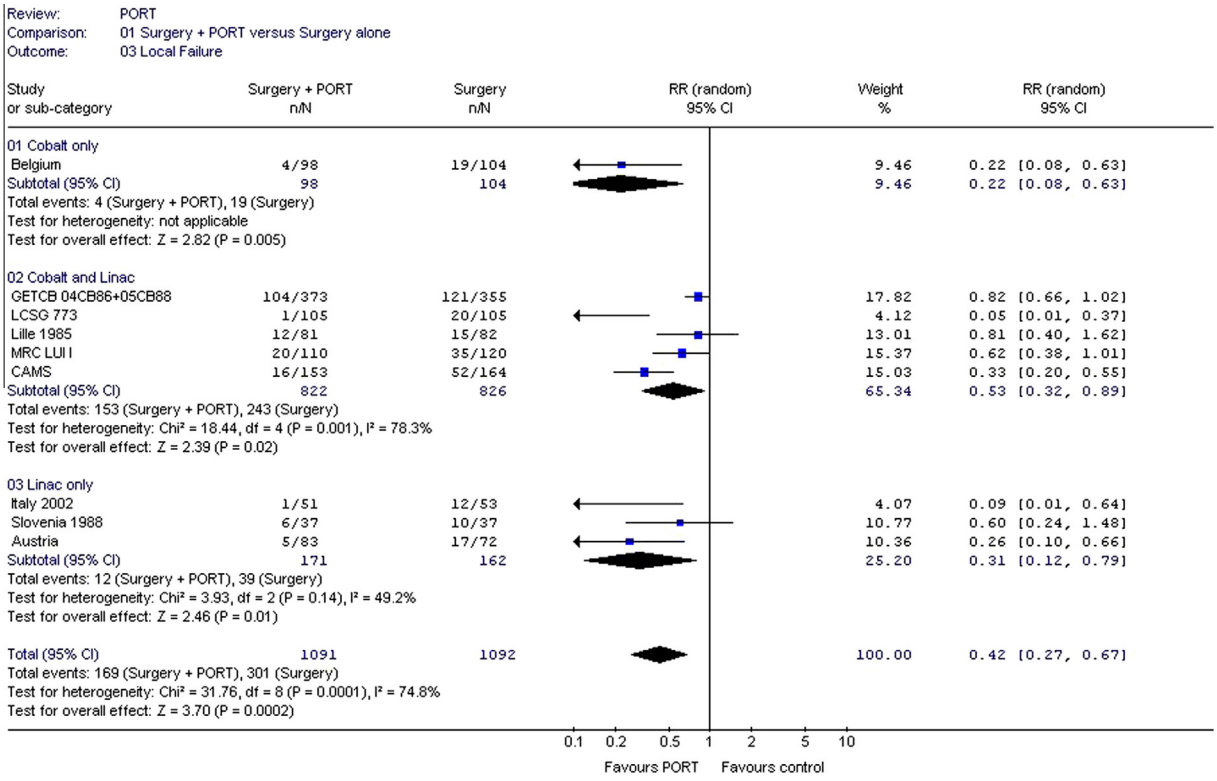

Fig. 1. Local tumor failure as a function of the beam quality used (copyright [13]). PORT: post-operative radiotherapy; RR: Relative Risk.