

Radiotherapy for single station N2 NSCLC

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Abstract: Clinical ‘single station N2’ is a prognostic factor, which is only moderately identifiable preoperatively, even after adequate mediastinal staging. There is little evidence that ‘single station N2’ predicts for the outcome of any radical treatment strategy, or for a benefit of postoperative radiotherapy. In adequately staged patients with clinical ‘single station N2’ involvement, modern definitive chemoradiation therapy results in equivalent outcome as induction therapy followed by resection.

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Introduction

According to the 7th TNM-staging classification of lung cancer, mediastinal lymph nodes are categorized in nine stations and three zones (1). Each station consists of several discrete lymph nodes, and an exact anatomical and radiological boundary between the mediastinal and hilar lymph node stations has been arbitrarily defined. When ipsilateral mediastinal lymph nodes are invaded this involvement is staged as N2. Ipsilateral refers to the location of the tumour with regard to the midline, which is located on the left border of the trachea.

Mediastinal lymph node invasion by lung cancer can be diagnosed either before, during or after a (planned) surgical treatment. Clinical N2 involvement refers to the evidence obtained with one of several different staging techniques including PET-CT scan, endoscopic ultrasound (EBUS or EUS) or mediastinoscopy. Pathological N2 involvement refers to the evidence obtained by microscopic examination of lymph nodes, obtained at therapeutic resection.

The American College of Chest Physicians (ACCP) distinguishes three types of mediastinal lymph node involvement in patients without distant metastases (2):

- (I) Pretreatment extensive mediastinal infiltration of tumor, whereby imaging assessment of the mediastinal stage is usually sufficient without invasive confirmation. This type of involvement falls outside

the scope of this manuscript and will not be further discussed;

- (II) Pretreatment discrete mediastinal lymph node enlargement on CT scan and/or FDG-PET uptake, to be confirmed by invasive techniques as mediastinoscopy or EUS, as neither imaging technique has a sufficient positive predictive value to exclude inflammatory causes;
- (III) Posttreatment occult N2 node involvement, despite thorough preoperative staging, found at operation or in the resection specimen.

Data from patients who have undergone primary surgical resection show that a lower burden of mediastinal lymph node involvement portends a better prognosis (3). This lower burden has been defined as clinical cN0/N1, single N2-station involvement or as intracapsular node involvement in older literature. In the database of the International Association for the Study of Lung Cancer (IASLC), resected patients with the involvement of a single N2 zone had a similar prognosis as those with involvement of multiple N1 nodes; their prognosis was furthermore intermediate between those who had N1 single-zone disease and those who had multiple N2 lymph node zones involved (4). Clinical involvement of a single N2 lymph node station has been associated with a better outcome by some (5-9) but not by others (10). The positive predictive value of the relationship between clinical and pathological lymph node

status is however, low (5), and the frequency of an R1 and R2 resection in patients with pN2 stage III NSCLC ranges from about 25% with thorough preoperative staging to 35% with poor preoperative staging (11).

Single station N2 is thus a prognostic factor, which is only accurately identifiable postoperatively. This manuscript will further review the evidence of (neo-)adjuvant radiotherapy in the treatment of single station N2.

Adjuvant radiotherapy in resected single station pN2

Several meta-analyses based on individual patient data of both published and unpublished trial data address the issue of postoperative radiotherapy (PORT) on the outcome of completely resected NSCLC (12-14). For the whole patient group, PORT decreased the survival at two years by 6% (52% *vs.* 58%). The deleterious effect of PORT has been attributed to an excess of intercurrent deaths, with a high incidence of cardiac and respiratory complications due to poor radiotherapy techniques (15,16). In support of this hypothesis, several more recent trials with contemporary radiation techniques did not report an increase of death from intercurrent disease (17-23). Epidemiological data from cancer registries and a subgroup analysis of a randomized trial investigating postoperative chemotherapy suggest even a possible benefit of PORT in pN2 patients (24-28).

The standard of care for fit patients with completely resected pIIIA-N2 is adjuvant platinum-based chemotherapy (2). The abovementioned meta-analyses do not rule out that there may be a role for PORT in patients with N2-disease. This issue is presently being addressed in the multicenter international LUNG ART trial (29). Patients found to have occult pN2 disease despite thorough preoperative staging, are likely to benefit from PORT, when concern for a local recurrence is high (2). This is the case with extracapsular spread of the tumour in the mediastinum (R1), or whenever multiple resected lymph node stations are involved. The lymph node ratio (LNR) is defined as the number of pathologically invaded lymph nodes divided by the total number of resected lymph nodes examined. In a multivariate analysis of PORT benefit for overall survival, stratified by pN stage and LNR, patients with pN2 disease and a LNR of 50% or more had significantly more benefit (30). In another series, the outcome of 50 resected patients with single station pN2 and of 41 others with multiple pN2 station involvement was analyzed according to the administration of PORT. Only

the latter group benefited from PORT (7).

The present evidence hence favours withholding PORT to patients with single station pN2.

Neo-adjuvant (chemo-)radiotherapy in pretreatment single station cN2

The ACCP guidelines recommend either definitive modern chemoradiation therapy or induction chemo(radio-) therapy followed by surgery over either surgery or radiation alone in patients with discrete N2 involvement, identified preoperatively (2). This recommendation is based on several randomized trials, in which no clear superiority of adjuvant surgery over definitive chemoradiotherapy could be evidenced. Modern chemoradiotherapy is given concurrently with a platinum doublet at full doses, and a total radiotherapy dose of 60-70 Gray (Gy) in continuous daily fractions of 1.8-2.0 Gy, using 3-dimensional conformal or intensity-modulated techniques.

Among the cited arguments justifying adjuvant surgery, is the presence of clinical single N2 lymph node station involvement. As mentioned earlier, this is also a prognostic factor, which is not accurately identifiable preoperatively. No data define whether the prognosis in these patients is further improved by the inclusion of surgery in their treatment strategy. Another concern is the out-of-context application of the available data: retrospectively derived results from one subgroup are applied directly to a different group (e.g., outcomes of occult single node N2 involvement do not appear to apply to patients with preoperatively identified single node N2 disease). The identification of patients more likely to benefit from resection after induction therapy is not possible based upon pretreatment characteristics and the role of surgery as part of the treatment plan for these subgroups is hence unclear at best.

Analysis of 41 NSCLC patients with a PET-scan- and/or EBUS-proven involved single N2 lymph node station and included in a prospective trial with chemo-radiotherapy using individualized isotoxic accelerated radiotherapy with concurrent or sequential platinum-based chemotherapy, showed a median overall survival of 26 months with 2- and 5-year survival rates of 53% and 24%, respectively (31). These data are comparable with a surgical single center series wherein patients with single station cN2 were resected after response to induction chemotherapy (10).

The present evidence suggest that, in adequately staged patients with clinical 'single station N2' involvement, modern definitive chemoradiation therapy results in an equivalent

outcome as induction therapy followed by resection, but with a lower morbidity.

Conclusions

Clinical 'single station N2' is a prognostic factor, which is only moderately identifiable preoperatively, even after adequate mediastinal staging. There is furthermore no evidence that 'single station N2' predicts for the outcome of any radical treatment strategy, nor for a benefit of PORT. Finally, in adequately staged patients with clinical 'single station N2' involvement, modern definitive chemoradiation therapy results in equivalent outcome as induction therapy followed by resection.

The treatment paradigm shift is that the lower the mediastinal lymph node tumor burden, the more effective chemoradiotherapy becomes. Surgery following chemotherapy should be restricted for those cases which cannot confidently be encompassed in a radiation portal or for salvaging relapsing cases.

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