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Phase II clinical trial

Target volume for postoperative radiotherapy in non-small cell lung cancer: Results from a prospective trial

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ABSTRACT

Background and purpose: A previous prospective trial reported that three-dimensional conformal postoperative radiotherapy (PORT) for pN2 NSCLC patients using a limited clinical target volume (CTV) had a late morbidity rate and pulmonary function that did not differ from those observed in pN1 patients treated with surgery without PORT. The aim of this study was to assess locoregional control and localization of failure in patients treated with PORT.

Materials and methods: The pattern of locoregional failure was evaluated retrospectively in 151 of 171 patients included in the PORT arm. The CTV included the involved lymph node stations and those with a risk of invasion >10%. Competing risk analysis was used to assess the incidence of locoregional failure and its location outside the CTV.

Results: Overall survival at 5 years was 27.1% with a median follow-up of 67 months for 40 living patients. The 5-year cumulative incidence of locoregional failure was 19.4% (95% CI: 18.2–20.5%) including a failure rate of 2% (95% CI: 0–17%) in locations outside or at the border of the CTV.

Conclusions: The use of limited CTV was associated with acceptable risk of geographic miss. Overall locoregional control was similar to that reported by other studies using PORT for pN2 patients.

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Improving the outcome of radiotherapy of lung cancer is a continuous challenge. Improved volume delineation may reduce treatment toxicity while increasing loco-regional control or at least keeping it constant [1–3]. However, a doubt persists if the limitation of target volume is always safe [4–6]. There is no clear consensus on the definition of the extent of the clinical target volume (CTV) for postoperative radiotherapy (PORT) because there is no evidence relating to this topic. The lack of agreement reflects controversy over the use of PORT itself. The value of PORT for non-small cell lung cancer (NSCLC) was questioned in a meta-analysis that compared the use of PORT with surgery alone [7] in 2128 patients from nine randomized trials. This meta-analysis found a 21% increased relative risk of death with the use of PORT. This deleterious effect was detected in patients with pN0-1 disease, but survival in patients with pN2 disease treated with PORT did not differ from that in patients not treated with PORT. This meta-analysis was updated in 2005, including one more trial; however, the main conclusions remained unchanged in comparison with a previous analysis. PORT was associated with a relative increase of the risk of death by 18% [8]. After these meta-analyses, the use of PORT was abandoned in many radiotherapy departments worldwide.

PORT represents a form of elective nodal irradiation (ENI), and this concept has been abandoned gradually in clinical practice despite a lack of clear evidence for such an approach [9]. It has been hypothesized that the toxicity reported in the meta-analysis mentioned above was related to large field sizes and to the use of obsolete radiotherapy techniques. It is believed that technical advances and modern radiotherapy planning may increase the therapeutic ratio of PORT [10–13]. The use of adjuvant chemotherapy in stage III disease prolongs survival [14]. It has been hypothesized that with the reduction of distant metastases with chemotherapy, the survival benefit by improved local control after three-dimensional conformal radiotherapy (3D-CRT) will occur. This hypothesis should be evaluated in randomized trials. Currently, two such trials, one from France and one from China are registered on the ClinicalTrials website http://clinicaltrials.gov under numbers NCT00410683 and NCT00880971, respectively (accessed in May 2013). Completion of one of those trials is expected in 2021.

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We have recently published the results from a prospective study that evaluated cardiopulmonary morbidity and quality of life (QoL) in completely resected pN2 patients treated with 3D-planned PORT using a limited CTV. Cardiac, respiratory symptoms, and pulmonary function tests (PFT) were evaluated and compared between pN2 patients treated with PORT and pN1 patients who did not receive PORT. PORT applied using contemporary techniques did not increase cardiopulmonary morbidity and did not impair PFT results and QoL at the evaluation performed two years after treatment. This technique was shown to be safe because no signs of late toxicity were demonstrated [15].

A concern is whether this technique is also efficacious in terms of locoregional control. Specifically, one may fear a high risk of geographic miss considering the use of limited ENI. To address this concern, we retrospectively assessed the locoregional control with a special focus on the locations of locoregional failure in relation to the CTV in patients treated within the study mentioned above [15].

Material and methods

The design and methods of treatment of the study has been previously reported in detail [15]. In short, NSCLC patients with nodal involvement confirmed by pathological examination following complete resection were included in the study in which pN1 patients were observed and pN2 patients were given PORT. Radiotherapy was planned using a 3D-planning system with heterogeneity correction. Only high-energy photon beams were allowed. To standardize the CTV delineation, a workshop for participating radiation oncologists was organized before the start of the study and once during the study. The CTV included the bronchial stump and lymph node stations (LNSs) with metastases in the pathological examination. Additionally, the uninvolved LNSs with the highest probability (>10% of risk [16]) of microscopic involvement were included, namely the ipsilateral hilum, subcarinal nodes (LNS 7), ipsilateral lower paratracheal lymph nodes (4R or 4L), LNS 3A up to top of aortic arch, and aortopulmonary window (LNS 5) for left sided tumors. The decision to include the ipsilateral supraclavicular region in case of pathologic invasion of LNS 1 or 2 was left to the discretion of the treating physician in the study protocol. Actually, the supraclavicular areas were not included into the CTV in any of the patients. Examples of CTV delineation are presented in Figs. 1 and 2. A 1 cm margin was added to CTV to create the planning target volume (PTV). The mean PTV was 333 cc and ranged from 113 to 789 cc. The prescribed total PTV dose was 54–56 Gy or less, but with a minimum dose of 50 Gy. In cases of extracapsular nodal extension of metastases, CTV-boost and PTV-boost were created by increasing the dose up to 60 Gy due to the increased risk of locoregional failure. Total dose was delivered in 2 Gy fractions five times a week. No central quality control for CTV contouring was performed.

After treatment, the patients were followed up according to the local policy at 3-month intervals. Two years after the surgery, the chest with upper abdomen CT and bronchoscopy were performed in all patients without previous diagnosis of a relapse. Two years posttreatment, the distant and locoregional relapse patterns were recorded along with cardiopulmonary morbidity [PFT results, symptom checklist] and QoL, which were the main end points of the previous study [15]. Locoregional failure was defined as a recurrence in the ipsilateral or contralateral hilum, mediastinum, supraclavicular area, or tumor bed (e.g., thoracic wall). Locoregional failure was recorded regardless of the presence of distant metastases. Pathological verification of the failure was not mandatory. For the purpose of the current study, survival and the occurrence of the locoregional and distant failures were up-dated. The loco-regional recurrences were categorized by local radiation oncologists into four groups: (1) occurring only within the CTV, (2) occurring both within and outside the CTV, (3) occurring only outside the CTV, and (4) occurring only at the border of the CTV. Locoregional failure occurring both within and outside the CTV was defined as multiple locoregional failure seen both within and outside the CTV, whereas a failure only at the border of the CTV was defined as a single lesion located partly within the CTV and partly outside the CTV. Recurrence was categorized based on the reports of the local radiologist. In cases when the location of the local recurrence in relation to the CTV could not be established from these reports, the location of the recurrence on radiological examinations was reevaluated by a local radiation oncologist and radiologist, and was compared with the volume contoured as the CTV. The decision about local recurrence category was then made.

Statistics

All time intervals were measured from the date of surgery. Overall survival was estimated using Kaplan–Meier method. To estimate the cumulative incidence of locoregional failure, the competing risk analysis method was used [17]. The competing event for the cumulative incidence of the total locoregional failure was death without locoregional failure. Competing events for the calculation of the cumulative incidence of locoregional failure outside or at the border of the CTV were death without locoregional failure, locoregional failure only within the CTV, and locoregional failure both within and outside the CTV.

Results

Between April 2003 and September 2007, 171 pN2 patients (PORT group) were included in the study from nine centers. Twenty patients (11.7%) were excluded from the analysis for the following reasons: eight patients received a dose <40 Gy, three patients died because of non-cancer causes within 1 month post-treatment, three patients were lost to follow-up, and six patients had mediastinal recurrence but the location of this recurrence (within or outside CTV) could not be established. The remaining 151 patients were included in the analysis. The median age was 61 years (range 40–78 years); 111 (73.5%) were men and 40 (26.5%) were women. Preoperative chemotherapy was received by 18 patients (11.9%) and postoperative chemotherapy by eight patients (5.3%). The types of surgery were pneumonectomy in 47 patients (31.3%), bilobectomy in eight patients (5.3%), lobectomy in 95 patients (63.3%), and no data in one patient. The histopathology was squamous cell carcinoma in 64 patients (42%), adenocarcinoma in 65 patients (43%), large cell carcinoma in six patients (4%), and other types of NSCLC in 16 patients (11%).

One-hundred-eleven (73.5%) patients died. The median follow-up for the 40 living patients was 67 months (range 13–106 months); 37 of these patients (92.5%) had a follow-up longer than 3 years. Actuarial overall survival at 5 years was 27.1% (95% CI 19.8–34.4%). Distant metastases alone or with local recurrence were recorded in 83 patients (55.0%). Locoregional recurrence was observed in 29 patients (19.2%). Fourteen of these patients (9.3%) had both, locoregional recurrence and distant metastases, and the other 15 patients had locoregional recurrence alone. Of the 29 patients with locoregional recurrence, 17 (11.3%) had recurrence only within the CTV, nine (6.0%) had recurrence both within the CTV and in the regional lymph nodes outside the CTV, and three (2.0%) had only regional recurrence outside the CTV ($n = 2$) or at the border of the CTV ($n = 1$). The cumulative incidence of the total number of locoregional failures at 5 years was 19.4% (95% CI 18.2–20.5%) for the study group and 22.5% (95% CI 21.4–23.6%) when six patients with an undetermined location of

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