Radiotherapy and Oncology 101 (2011) 278–283

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Chemoradiotherapy of lung cancer

Concurrent high-dose radiotherapy with low-dose chemotherapy in patients with non-small cell lung cancer of the superior sulcus

Ingrid Kappers [a,*], Houke M. Klomp [a], Mia G.J. Koolen [b], Lon J. Uitterhoeve [c], Jaap J. Kloek [d], José S.A. Belderbos [e], Jacobus A. Burgers [f], Caro C.E. Koning [c]

[a] Department of Surgery, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; [b] Department of Pulmonology; [c] Department of Radiation Oncology; and [d] Department of Surgery, Academic Medical Centre Amsterdam, The Netherlands; [e] Department of Radiation Oncology; and [f] Department of Thoracic Oncology, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 25 July 2010
Received in revised form 29 March 2011
Accepted 12 May 2011
Available online 30 June 2011

Keywords:
Non-small cell lung cancer
Sulcus superior tumours
Chemoradiotherapy
Surgery
Multimodality treatment

ABSTRACT

Background and purpose: In the treatment of patients with tumours of the sulcus superior (SST), achieving local control is essential because residual or recurrent disease is associated with severe locoregional problems. This study evaluates the efficacy of concurrent daily low-dose cisplatin (6 mg/m^2) and high-dose radiotherapy (66 Gy) followed by surgical resection in selected patients.

Material and methods: Clinical charts, imaging and pathology reports were retrospectively reviewed. Survival was analysed using the Kaplan–Meier method.

Results: Forty-nine patients with stage II/III SST were treated with concurrent high-dose radiotherapy and low-dose chemotherapy (CRT). Mean follow-up was 49 months (range 2–152).

Results: Nineteen patients underwent additional resection after CRT. In 53% a pathological complete response (pCR) was observed (10/19pts). Acute severe toxicity occurred in 49% (9/19pts). Late severe toxicity occurred in 3 patients. The 2- and 5-year overall survival was 74% and 33%, respectively. Local tumour control was 100%. Thirty patients received CRT only. Acute severe toxicity occurred in 23% (7/30pts). Treatment-related mortality was 2%. The 2- and 5-year overall survival was 31% and 18%, respectively. Locoregional disease-free survival was 48% at 5 years.

Conclusions: Concurrent high-dose (66 Gy) radiotherapy and daily low-dose cisplatin was associated with a high pCR rate. Excellent local control was achieved after additional resection in selected patients. However, the occurrence of severe toxicity in long-term survivors after concurrent chemoradiation followed by surgery must be considered.

 Radiotherapy and Oncology 101 (2011) 278–283

Superior sulcus tumours are mostly non-small cell lung cancers (NSCLC) located in the apex of the lung. By definition they invade the adjacent chest wall in the superior pulmonary sulcus [1]. Vital structures like brachial plexus, subclavian vessels, vertebral column and spinal cord are near and therefore often threatened or involved. Radical treatment for superior sulcus tumours is complex, since their particular locations near vital structures often prohibit safe resection margins or high doses of radiotherapy. However, achievement of local control is crucial, because residual or local recurrent disease is associated with severe pain. Neoadjuvant treatment is therefore advocated to ensure radical treatment.

Significant progress has been made in the development of neoadjuvant treatment of superior sulcus tumours throughout the last decades [2]. In 1992, the first phase III trial using concurrent chemoradiotherapy in NSCLC showed that daily low-dose chemotherapy (cisdiamminedichloroplatin or cDDP or cisplatin) and radiotherapy yielded better survival than radiotherapy alone [3]. Several subsequent reports have described a variety of concurrent chemoradiotherapy schemes, combining gradually higher radiotherapy doses with low-dose single agent chemotherapy or with high dose multi drug combinations [4–6]. Although the exact mechanism is not clear, daily (low-dose) chemotherapy improves local tumour eradication, as a radiotherapy sensitizer, whereas high-dose and multi-drug-combinations of chemotherapy are mainly directed towards elimination of distant (micro)metastases. In the latter, however, toxicity further limits the maximal feasible radiotherapy dose [6].

Since the main problem of superior sulcus tumours is their locoregional growth, high-dose radiotherapy and daily low-dose cDDP is regarded as the optimal induction regimen of choice in our practices. The aim of this study is to report our long term experience with concurrent chemoradiotherapy using high-dose radiotherapy (66 Gy, 24 fractions) and daily low-dose cDDP (6 mg/m^2) for patients with NSCLC of the superior sulcus [7].

* Corresponding author. Address: The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Department of Surgical Oncology, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands.
E-mail address: i.kappers@nki.nl (I. Kappers).

0167-8140/$ - see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.radonc.2011.05.030

Materials and methods

Patients

Patients with non-small cell lung cancer invading the superior sulcus who were referred from 1994 to 2006 to The Netherlands Cancer Institute and Academic Medical Centre Amsterdam formed the basis of this retrospective study. The study was approved by the Institutional Review Board. Some of these patients were described in a previous report, which focussed on selection of patients for different treatment modalities [8]. Age, gender, smoking status, performance status, pulmonary function, histological subtype, type of treatment, clinical and pathological tumour stage, date and site of first relapse, and clinical and pathological response to treatment were retrieved from the patient charts. Toxicity was assessed using the NCI Common Terminology Criteria v 3.0.

The diagnosis was histologically confirmed after CT scan and bronchoscopy. Positron emission tomography ([^{18}F]-FDG-PET) was frequently used since its introduction in the year 2000, and became standard in the year 2002. Mediastinoscopy was performed when pathological mediastinal lymph nodes were suspected on CT scan, unless a PET scan showed no mediastinal metabolic activity. In more recent years, oesophageal ultrasonography with fine needle aspiration (EUS-FNA) was used (since the year 2002), to replace or complement mediastinoscopy in staging the mediastinum. MRI was used to determine tumour involvement of the vertebrae, brachial plexus, and subclavian vessels in patients who were candidates for surgery. All patients were discussed in our multidisciplinary thoracic oncological team to assess tumour stage and to decide on the treatment plan.

Primary treatment strategy

The majority of patients were ineligible for surgery. They were either medically inoperable or their tumours were considered irresectable, even after induction treatment. Depending on their medical condition, they received RT with or without the addition of chemotherapy (CT). The preferred regimen was concurrent CRT (66 Gy + daily cisplatin 6 mg/m^2). Contraindications for this concurrent chemoradiotherapy (CRT) scheme were a performance status of WHO > 2, weight loss of > 10% of the original weight, or insufficient renal function.

Concurrent chemoradiotherapy was the preferred induction regimen if surgical resection was considered feasible. In both centres a concomitant boost technique was used to a total dose of 66 Gy in 24 fractions of 2.75 Gy within 32 days [4], combined with daily low-dose cisplatin of 6 mg/m^2, given intravenously 1–2 h before each fraction of radiotherapy. This regimen was extensively studied in two trials by Uitterhoeve and Belderbos [4,7]. In earlier years, doses of 55 Gy in 20 fractions were used, but from the year 1996 on 66 Gy in 24 fractions (less than 5 weeks) appeared to be feasible and became standard [3,4].

All patients were treated with megavoltage photon beams $\geqslant$ 5 MV energy. The Gross Tumour Volume (GTV) was defined as the primary tumour and lymph nodes with a short axis of $\geqslant$ 1 cm on the CT scan. The Elective Planning Target Volume (EPTV) encompassed GTV and the first lymph node drainage group not considered as pathological plus a margin of 1.5 cm. The Boost Planning Target Volume (BPTV) included the GTV with a 1 cm margin of normal tissue.

To irradiate the EPTV two opposite anterior–posterior–posterior–anterior (AP–PA fields) or a multiple beam arrangement were used. The prescribed dose was 40 Gy in 20 fractions of 2 Gy given five times a week. The dose was defined according to the ICRU 50 report. The BPTV was irradiated with 3-dimensional conformal radiotherapy. The daily dose to the BPTV was 0.75 Gy given concurrently with the treatment of the EPTV during the first 20 fractions.

After a total dose of 55 Gy (20 fractions), four additional fractions were administered to the BPTV with 2.75 Gy per fraction up to 66 Gy. With the introduction of PET scanning the radiotherapy fields encompassed the involved areas only.

The accelerated irradiation course of 66 Gy in 24 fractions of 2.75 Gy within 32 days that was used in this study, compares to a radiobiologically equivalent dose of 72 Gy/2 Gy. All patients were irradiated with 3D conformal radiotherapy. The following limits according to the tolerance of organs at risk were used: spinal cord dose < 50 Gy, mean lung dose < 16 Gy and the V35 oesophagus < 65%. For the heart the maximum dose allowed was 40 Gy for the whole heart, 50 Gy for 2/3 of the heart and 66 Gy for 1/3 of the heart. All tolerance doses mentioned are normalised total doses.

Restaging and surgery

Three to four weeks after completion of the chemoradiation treatment response was evaluated using CT and MRI scans, according to the unidimensional RECIST criteria [9]. Unless progressive disease (PD) was detected, the response observed on radiological imaging did not affect the evaluation of resectability. Restaging of the mediastinum was done using mediastinoscopy if (persisting) N2 disease was suspected on CT scan (re-mediastinoscopy was avoided). Surgery was scheduled 4–6 weeks after completion of chemoradiotherapy, and generally consisted of en-bloc resection of the affected lobe and chest wall structures. Mediastinal lymph node sampling was carried out in all patients.

The majority of patients were ineligible for surgery. They were either medically inoperable or their tumours were considered irresectable, even after induction treatment.

Patients were followed according to a standard follow-up scheme every 3 months during the first year, every 6 months during the second and third year, and every twelve months thereafter. Chest X-ray was commonly performed, and, if clinically indicated, was followed by CT scan. Survival was calculated using the Kaplan–Meier method from the date of diagnosis. For the analysis of (disease-free) survival, events were defined as recurrent disease – due to distant metastasis or locoregional recurrence – or death due to disease progression or any other cause.

Results

From 1994 to 2006, 115 patients with superior sulcus tumours were referred to the Academic Medical Centre Amsterdam and The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital. Fig. 1 shows the treatment chart of all 115 patients. Of the 93 patients with stage II and III disease, 49 patients were treated with concurrent CRT, either preceding surgery (n = 19) or as definitive treatment (n = 30). These 49 patients form the subject of this report, and will be discussed separately in two sections.

Mean follow-up of all 49 patients was 49 months (range 2–152 months). Follow-up was complete until January 2009 for all patients except one who was lost to follow-up after 2 months. Patient characteristics are shown in Table 1. Eighteen patients had stage IIB, 4 patients stage IIIA, and 27 patients stage IIIB. There were 22 cT3 and 27 cT4 tumours diagnosed on pre-treatment staging. In 27 of 49 patients, mediastinal lymph nodes were negative on PET/CT scan. In 11 patients, mediastinal lymph nodes were not pathologically enlarged (<1 cm) on CT. In 11 patients mediastinoscopy was performed and revealed ipsilateral mediastinal lymph node metastases (N2 disease) in 2 patients and contralateral lymph node metastasis in 1 patient (N3 disease).