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Long-term survival of stage T4N0-1 and single station IIIA-N2 NSCLC patients treated with definitive chemo-radiotherapy using individualised isotoxic accelerated radiotherapy (INDAR)

Bart Reymen [a,*], Angela van Baardwijk [a], Rinus Wanders [a], Jacques Borger [a], Anne-Marie C. Dingemans [b], Gerben Bootsma [c], Cordula Pitz [d], Ragnar Lunde [e], Wiel Geraedts [f], Philippe Lambin [a], Dirk De Ruysscher [a,g]

[a] Department of Radiation Oncology (MAASTRO Clinic); [b] Department of Pulmonology, University Medical Centre Maastricht, GROW-School for Oncology and Developmental Biology; [c] Department of Pulmonology, Atrium Medical Centre, Heerlen; [d] Department of Pulmonology, Laurentius Hospital, Roermond; [e] Department of Pulmonology, St. Jansgasthuis, Weert; [f] Department of Pulmonology, Orbis Medical Centre, Sittard, The Netherlands; [g] University Hospital Leuven/KU Leuven, Belgium

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ABSTRACT

Background: Non-small cell lung cancer (NSCLC) stage T4N0-1 or single nodal station IIIA-N2 are two stage III sub-groups for which the outcome of non-surgical therapy is not well known. We investigated the results of individualised isotoxic accelerated radiotherapy (INDAR) and chemotherapy in this setting.
Methods: Analysis of NSCLC patients included in 2 prospective trials (NCT00573040 and NCT00572325) stage T4N0-1 or IIIA-N2 with 1 pathologic nodal station, treated with chemo-radiotherapy (CRT) using INDAR with concurrent or sequential platinum-based chemotherapy. Overall survival (OS) was updated and calculated from date of diagnosis (Kaplan–Meier). Toxicity was scored following CTCAEv3.0. To allow comparison with other articles the subgroups were also analysed separately for toxicity, progression free and overall survival.
Results: 83 patients (42 T4N0-1 and 41 IIIA-N2) were identified: the median radiotherapy dose was 65 Gy. Thirty-seven percent of patients received sequential CRT and 63% received concurrent CRT. At a median follow-up of 48 months the median OS for T4N0-1 patients was 34 months with 55% 2-year survival and 25% 5-year survival. For stage IIIA-N2 at a median follow-up of 50 months the median OS was 26 months with 2- and 5-year survival rates of 53% and 24%, respectively.
Conclusion: Chemo-radiation using INDAR yields promising survival results in patients with single-station stage IIIA-N2 or T4N0-1 NSCLC.

The treatment of non-small cell lung cancer (NSCLC) stage T4N0-1 and stage IIIA-N2 with a single involved mediastinal nodal station is controversial. Although concurrent chemo-radiotherapy (CRT) is considered standard treatment for stage III NSCLC, some still advocate surgery combined with chemotherapy as the only treatment option capable of generating long-term survival in these subgroups with "potentially resectable", low-volume disease [1]. There are indeed many publications reporting surgical results for these subgroups, while prospective data on modern CRT are lacking [2–9]. To the best of our knowledge no data are available about the prognosis of a homogenous group of patients with single-station N2 or T4N0-1 NSCLC. Current radiotherapy series generally report on the whole group of mostly irresectable stage IIIA and IIIB NSCLC, but not on specific subgroups [10]. However, information about these particular subsets is crucial to enable a comparison of surgery to radiotherapy as local treatment. Even in the absence of phase III studies specifically designed for this purpose, knowledge of the potential outcome of patients with single-station N2 disease or T4N0-1 NSCLC can help clinicians to propose treatment choices to their patients.

Patients and methods

Patient population

We have previously reported on two prospective trials (NCT00573040 and NCT00572325) using individualised isotoxic accelerated radiotherapy (INDAR) with chemotherapy in NSCLC [11,12]. We now performed a subgroup analysis of these trials on patients staged T4N0-1 or IIIA-N2. All diagnostic images and pathology reports were checked to verify T4 status and if only one N2 station was involved. Patients included had an adequate

* Corresponding author.
E-mail address: bart.reymen@maastro.nl (B. Reymen).

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lung function (FEV-1 and DLCO $\geqslant$30% predicted), WHO-PS $\leqslant$2 and <10% weight loss over 6 months.

Staging

Staging was done following national guidelines with a whole body ^{18}F-deoxyglucose (FDG)-Positron Emission Tomography (PET) scan, calibrated according to the NEDPAS protocol [13] and a contrast enhanced brain CT or MRI [5]. The diagnosis was pathologically confirmed in all patients. Each case was discussed by a multidisciplinary board including a pulmonologist, thoracic surgeon, pathologist, nuclear medicine physician, radiologist and a radiation oncologist.

T4 status was evaluated on imaging and defined according to the UICC TNM classification (fifth edition), excluding malignant pleural effusion. Patients considered fit for surgery underwent invasive mediastinal staging. Nodal involvement was pathologically confirmed whenever possible.

Chemotherapy

In our region stage III NSCLC was treated with sequential CRT up to 2005. In 2006 concurrent CRT was gradually introduced to become standard treatment from 2008 onwards. As previously described standard chemotherapy in sequential schedules was 3 courses of cisplatin (75 mg/m^2 on day 1) combined with gemcitabine (1250 mg/m^2 on days 1 and 8). For concurrent CRT 1 cycle of carboplatin–gemcitabine (carboplatin AUC 5, gemcitabine 1250 mg/m^2) was given before the onset of radiotherapy followed by 2 cycles of cisplatin–vinorelbine (cisplatin 40–50 mg/m^2, vinorelbine 15–20 mg/m^2) or cisplatin–etoposide (cisplatin 75–80 mg/m^2 day 1, etoposide 100 mg/m^2 days 1–3) concurrently with radiotherapy [11,12]. Standard dose reduction rules applied. Cisplatin was switched to carboplatin (area under the concentration–time curve [AUC] 5) in patients with renal impairment.

Radiotherapy

All patients received a contrast enhanced FDG PET–CT scan in treatment position (supine, arms raised) using a slice thickness of 3 mm for radiation treatment planning. Respiratory correlated CT (RCCT) images were also collected starting from April 2006.

Gross tumour volume (GTV-1) delineation was done on the RCCT images using appropriate window-level settings (lung: $W = 1700$, $L = -300$, mediastinum: $W = 600$, $L = 40$), aided by FDG-PET. Involved hilar/mediastinal lymph nodes (GTV-2) were delineated on the RCCT in mediastinal setting. FDG-PET-negative nodes were not included in GTV-2 unless pathologically proven to be malignant. The CTV-margin was 5 mm for GTV-1 and GTV-2 excluding vessels, bone and oesophagus. The CTV did not include elective nodal areas. PTV-margin was 5 mm for nodes and 10 mm for tumour. The healthy lung tissue (lungs-GTV), spinal cord and oesophagus were considered organs at risk. In patients treated with sequential chemotherapy, the post-chemotherapy tumour volume was defined as GTV and the included nodal areas were defined as staged pre-chemotherapy (PET-positive and/or pathology proven before start of chemotherapy).

Planning was performed on XIO (CMS, St. Louis) using a convolution-superposition algorithm for inhomogeneity correction. Standard radiotherapy consisted of INDAR up to a maximal total tumour dose (TTD) limited only by normal tissue dose constraints which was described in previous publications [11,12]. In short, 2 fractionation schedules were used. Concurrently with chemotherapy, the accelerated radiotherapy scheme was based on the ESPATÜ phase III trial scheme. It consisted of 30 fractions of 1.5 Gy twice daily (bid), followed by daily fractions of 2 Gy up to a maximal TTD limited by the normal tissue constraints between 51 and 69 Gy. In this schedule a TTD of 65 Gy delivered in an OTT of 35 days matches a biological EQD2 corrected for time of 54 Gy, corresponding to a dose of 72 Gy in 2 Gy fractions delivered in 50 days. This was calculated according to the linear quadratic model, corrected for overall treatment time:

$$EQD_{2,T} = D \bullet \frac{d + (\alpha/\beta)}{2 + (\alpha/\beta)} - (T_{ref} - T) \bullet D_{prolif}$$

We use an α/β ratio of 10 Gy for tumour, a T_{ref} of 21 days and an assumed daily recovered dose in 2-Gy equivalent fractions after 21 days (D_{prolif}) of 0.6 Gy [11,12,14]. In sequential schedules we delivered 1.8 Gy fractions bid up to a TTD between 50.4 and 70.2 Gy. In this schedule a TTD of 65 Gy delivered in an OTT of 25 days matches an EQD2 corrected for time of 61 Gy. According to the same formula, this corresponds to a dose of 82 Gy in 2 Gy fractions. Normal tissue constraints were: maximal point dose (D_{max}) for spinal cord = 54 ± 0.5 Gy, mean lung dose (MLD) 19 ± 1 Gy, D_{max} for vessels/bronchi = 74 Gy, D_{max} for brachial plexus = 66 Gy [11,12]. Treatment verification was performed using daily electronic portal imaging device measurements on each fraction, using set-up correction based on bony anatomy.

Follow-up

Patients were examined by the radiation oncologist 2–4 weeks after radiotherapy and followed until acute side-effects subsided to grade 1. Afterwards the pulmonologist followed patients three-monthly for the first year, six-monthly from years 2 to 5 and yearly thereafter. Chest CTs and X-rays were performed routinely. If progression was suspected a (PET-) CT was performed, complemented with biopsy if indicated. Toxicity was scored by clinicians at each visit (at baseline, during treatment and follow-up) according to CTC AE 3.0. The survival status of patients was updated in May 2013.

Statistics

Overall survival (OS) and progression-free survival (PFS) were calculated from pathological diagnosis using Kaplan–Meier statistics (SPSS version 17.0, IBM). Median survival rates are expressed together with their 95% confidence intervals (CI), other results as mean ± standard deviation and range. In this article follow-up is defined as follow-up of surviving patients.

Results

We identified 83 patients: 42 (34 male, 8 female) with T4N0-1 and 41 (24 male, 17 female) with single-station IIIA-N2 NSCLC. In 32 of 41 patients (78%) with clinical single-station N2 disease, this was pathologically confirmed. In the remaining patients this was suspected on the PET–CT. Six out of 42 patients (14%) had invasive confirmation (mediastinoscopy/thoracotomy) of T4 status. Patient characteristics are summarised in Tables 1A and 1B.

At a median follow-up of 41 months local tumour failure occurred in 18 patients with T4N0-1 tumours (43%). In 6 patients this remained the only disease site throughout follow-up. Regional nodal failure occurred in 5 patients (12%), all of whom were previously staged T4N0 and in all 5 patients simultaneous local tumour progression was present. Distant metastases occurred in 20 patients (47%), involving brain metastases in 11 patients (26%). Brain metastases were the first site of failure in 7 patients (17%).

At a median follow-up of 39 months, local tumour failure occurred in 10 patients with stage IIIA-N2 disease (24%) which was

Table 1a
Patient and treatment characteristics T4.

Characteristics	Median/n° ± SD	Range/(%)
Age	62.5 ± 9	44–80
Gender		
Male	34	(81)
Female	8	(19)
WHO-PS		
0	17	(40)
1	21	(50)
2	3	(8)
3	1	(2)
UICC TNM stage		
cT4N0M0	36	(85)
cT4N1M0	6	(15)
Class of T4		
Mediastinal invasion	35	(83)
2 Nodules in same lobe	1	(2)
Vertebral invasion	4	(10)
Mediastinal invasion +2 nodules same lobe	2	(5)
Chemotherapy		
Sequential	16	(38)
Concurrent	26	(62)
GTV (in cc)	80 ± 109.5	5.5–510
MLD (in Gy)	15 ± 4.4	5–19.9
Prescribed TTD (in Gy)	65.0 ± 7.3	50.4–79.2
Delivered TTD (in Gy)	65.0 ± 10	21.6–79.2
OTT (in days)	30.5 ± 7.5	9–42

Abbreviations: WHO-PS = World Health Organisation-Performance Status, GTV = Gross Tumour Volume, UICC = Union Internationale Contre Cancer, TNM = tumour, node, metastasis, Gy = Gray, TTD = total tumour dose, OTT = overall treatment time.
Values in parentheses are percentages.

Table 1b
Patient and treatment characteristics IIIA-N2.

Characteristic	Median/n° ± SD	Range/(%)
Age	64 ± 9	44–78
Gender		
Male	24	(59)
Female	17	(41)
WHO-PS		
0	17	(41)
1	21	(51)
2	3	(7)
UICC TNM stage		
cT0N2M0	3	(7)
cT1N2M0	12	(29)
cT2N2M0	20	(49)
cT3N2M0	6	(15)
Involved nodal station		
7	20	(49)
4R	6	(15)
4L	1	(2)
2R	2	(5)
5	11	(27)
8	1	(2)
Chemotherapy		
Sequential	15	(37)
Concurrent	26	(63)
GTV (in cc)	44.21 ± 90.5	3.4–440
MLD (in Gy)	14.5 ± 3.3	7–21
Prescribed TTD (in Gy)	65 ± 6	50.4–72
Delivered TTD (in Gy)	65 ± 6.8	43.5–72
OTT (in days)	30 ± 6.7	17–48

Abbreviations: WHO-PS = World Health Organisation-Performance Status, GTV = Gross Tumour Volume, UICC = Union Internationale Contre Cancer, TNM = tumour, node, metastasis, Gy = Gray, TTD = total tumour dose, OTT = overall treatment time.

radically treated with re-irradiation in one patient. Regional nodal failure occurred in 7 patients (17%). Four out of 7 patients relapsed outside the PTV. In all 7 patients, nodal failure either coincided with or was preceded by local or distant failure. Twenty-two patients (53%) developed distant metastases during follow-up. In 18 patients (44%) metastases were present at the initial time of diagnosis of progression. Ten patients (24%) were diagnosed with brain metastases, being the first site of failure in 7 patients (17%). Patterns of failure and actuarial loco-regional progression free survival for both groups are summarised in Table 2A and B and Fig. 2.

In patients with T4N0-1 tumours the median actuarial OS was 34 ± 7.5 months (19.6–48.8 months) at a median follow-up of 48 months (65 months for sequential and 46 months for concurrent chemo-radiation with a 2- and 3-year survival of 55% and 44%, respectively. Median actuarial PFS was 15 ± 0.7 months (9.7–20.2 months) with a 2- and 3-year PFS of 39% and 34%, respectively. The estimated 5-year survival is 25%. For patients treated with sequential CRT the median OS was 27 ± 7 months (13.3–40.7 months) compared with a median OS of 55 ± 24 months (7.9–102.1 months) for patients treated concurrently. Fig. 1 shows the overall survival curves for both groups.

The median follow-up of patients with stage IIIA-N2 disease was 50 months (70 months for sequential chemo-radiation and 41 months for concurrent chemo-radiation). The median actuarial OS for this group of patients was 26 ± 5.3 months (15.6–36.4 months) with a 2- and 3-year OS of 53% and 37%, respectively. Five-year survival is estimated at 24%. One patient was lost to follow-up and censored for progression 11 months after diagnosis. Median PFS was 24 ± 7.4 months (9.4–38.5 months) with a 2- and 3-year PFS of 51% and 31%, respectively. For patients treated with sequential or concurrent CRT median OS was 26 ± 6.7 months (13.3–38.6 months) and 23 ± 9.3 months (4.6–41.3 months), respectively.

In the group of T4N0-1 patients, 1 patient (2%) experienced grade 3 dyspnoea caused by pulmonary embolism during radiotherapy, which subsided to grade 0 at 1 month after therapy. Interestingly, dyspnoea was present in 38% of patients before therapy, while 1 month after therapy this was only 16%. One patient (2%) developed grade 3 cough which resolved at 1 month after radiotherapy.

The most frequent severe side-effect was grade 3 esophagitis. This occurred in 7 patients (17%) of whom 6 received concurrent CRT. In 5 patients tube feeding was initiated (12%) which lasted for more than 1 month in 1 patient, namely until 6 weeks post-treatment. In the cohort of patients with stage IIIA-N2 disease 7 patients (17%) developed grade 3 dysphagia during radiotherapy which required tube-feeding in 5 patients (12%). One patient had grade 3 dysphagia until 8 weeks post-radiotherapy. All other patients had grade 0–1 dysphagia at 1 month post-radiotherapy. One patient developed grade 4 dyspnoea due to cardiac failure during chemotherapy administration. One patient still suffered from grade 3 dyspnoea at 1 month after treatment due to pneumonia and cardiac arrhythmia complicated with pulmonary embolism. Four patients developed grade 3 cough. Two out of these 3 patients still presented with grade 2 cough at 1 month after radiotherapy. In all patients this complaint had resolved 2 months after treatment.

Discussion

Although standard treatment for most stage III NSCLC patients is concurrent chemo-radiotherapy, to the best of our knowledge

Table 2
Patterns of relapse.

Recurrence	Number of patients (%)	
	T4	IIIA-N2
No	15 (36)	18 (44)
Yes	27 (64)	23 (56)
Local tumour failure	18 (43)	10 (24)
Local failure + regional/distant failure	12 (29)	8 (19)
Isolated local tumour failure	6 (14)	2 (5)
Regional nodal failure	5 (12)	7 (17)
Nodal + local/distant failure	5 (12)	7 (17)
Isolated nodal failure (in field)	0 (0)	0 (0)
Distant failure	20 (48)	22 (54)
Distant + local/regional failure	11 (26)	12 (29)
Isolated distant failure	9 (21)	10 (24)
Isolated brain metastases	5 (12)	3 (7)

Location of relapses assessed with CT. Numbers between parentheses are percentages.

no data are available on the outcome of the N2 or T4N0-1 subgroups which are frequently considered surgical candidates. This perception is based on numerous surgical series reporting median survival of 20–43 months and 5-year survival rates from 24% up to 43% and an absence of radiotherapy data in these specific patients [2,4–9,15,16].

This report reflects our current institutional policy through subgroup analysis of two prospective phase II trials. Since 2005 we use INDAR, delivering the highest dose of accelerated radiotherapy without exceeding normal tissue dose constraints, generating good survival results with acceptable toxicity [11,12,17]. Our median OS for T4N0-1 and single station IIIA-N2 of respectively 34 and 26 months and estimated 5-year survival of 25% and 24% compare well with surgical literature [2,4,5,8,9,15,16], albeit having the advantage of PET-staging, which was not the case for most other studies. Our results in the IIIA-N2 cohort compare especially well with the two major randomised trials which have compared surgery to radiotherapy for stage IIIA-N2 NSCLC. EORTC 08941 randomised patients with unresectable stage IIIA-N2 NSCLC to surgery or radiotherapy after response to induction chemotherapy. Median survival in 165 patients treated with radiotherapy was 17.5 months and 5-year survival was 14% with a median PFS of 11.3 months [18]. In Intergroup 0139 patients with resectable stage IIIA-N2 were randomised between either definitive concurrent chemo-radiation to induction chemo-radiation followed by surgery. Seventy-five percent of patients in both groups had a single nodal station involved. Median survival after radiotherapy was 23.6 months with a median PFS of 12.8 months and a projected 5-year survival of 20–25% [10]. Both trials found no significant difference in overall survival between surgery and radiotherapy.

Local tumour failure was more frequent in stage T4 (43%) than in IIIA-N2 patients (22%). A possible explanation is the median volume of the primary T4 tumours, which was twice that of the N2 patients, which is known to heavily impact tumour control in NSCLC [19,20]. This remains worrisome and needs improvement, possibly by further radiation dose escalation or selective combination with surgery or targeted agents [21]. Despite omission of elective nodal radiotherapy nodal recurrence rate was low.

Distant metastases are the predominant way of disease progression, occurring in about 50% of patients, with brain metastases appearing in 25%. This emphasises both the need for better systemic treatment and prevention of brain metastases.

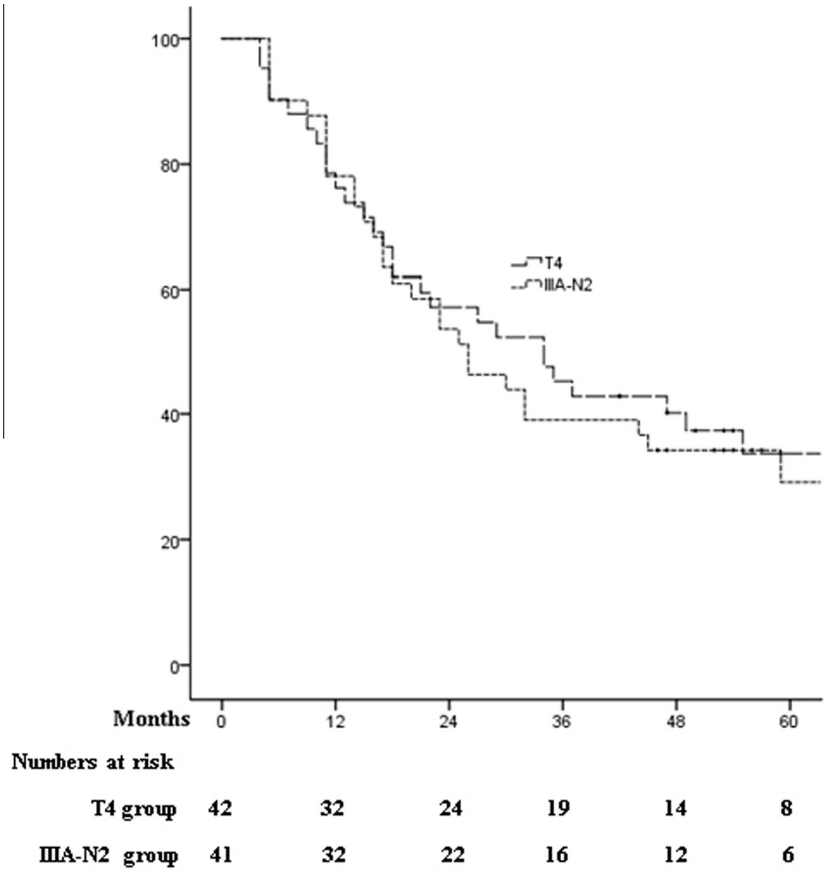

Fig. 1. Overall survival (Kaplan Meier). Actuarial overall survival of 42 T4N0-1 patients and 41 single nodal station stage IIIA-N2 patients.

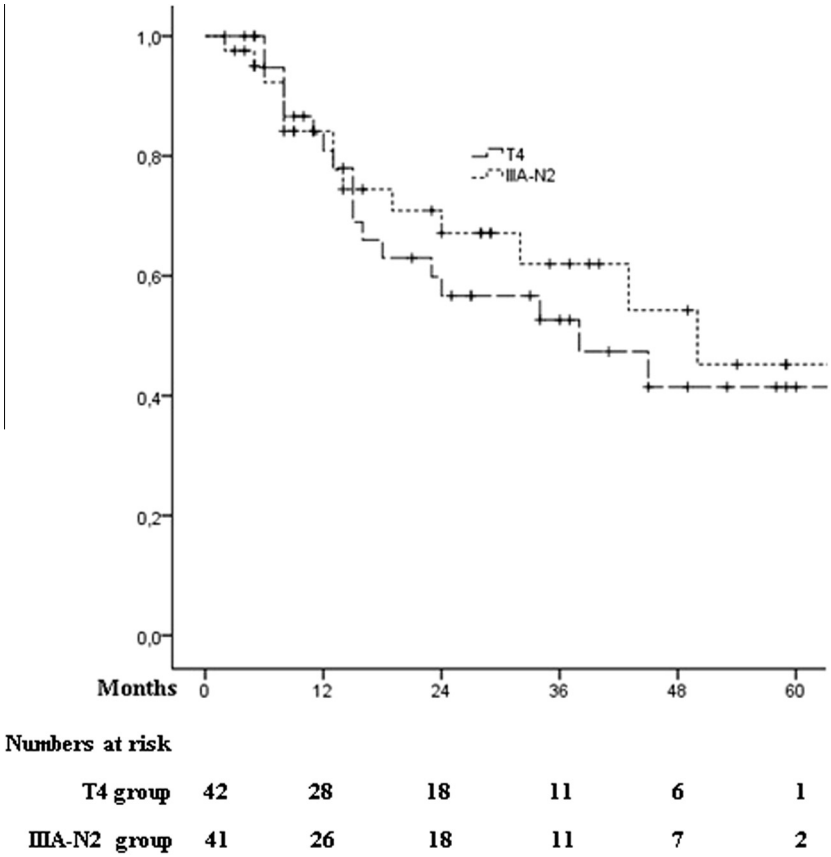

Fig. 2. Loco-regional progression free survival (Kaplan Meier). Actuarial rates of loco-regional progression free survival for 42 T4N0-1 patients and 41 single nodal station stage IIIA-N2 patients.

Toxicity was acceptable with grade 3 esophagitis occurring in 17% of patients, which is in line with literature on CRT for stage III NSCLC [10]. Treatment related mortality occurring within one month of treatment was low (1/83, 1%).

This study has some obvious shortcomings. First, T4 staging was mainly FDG-PET-CT based. Although contrast-enhanced PET-CT reportedly has a > 90% accuracy for defining T stage, some patients might ultimately have had pT3 and not pT4 tumours [22]. Second, we report on both concurrent and sequential chemo-radiotherapy, admitting the former to obviously being the standard treatment for fit patients with a stage III NSCLC. However, in worldwide clinical practice still a fairly large proportion of inoperable patients receive sequential CRT based on clinical judgment by treating physicians [23]. Third, although most stage IIIA-N2 patients had pathological validation of N2 status, invasive mediastinal staging (mediastinoscopy) was not routinely performed, which may have led to nodal understaging. A final comment is that the tumour with 2 nodules in the same lobe which was classified as T4 would be considered T3 in the current (seventh) TNM staging system. We have kept this patient in the analysis to allow comparison with most other articles on surgery or radiotherapy for T4 NSCLC which have also made use of the TNM fifth or sixth edition.

Keeping all caveats in mind, this study shows that accelerated, individualised CRT is a valuable treatment option for T4N0-1M0 and single-station IIIA-N2 NSCLC, achieving long-term survival in about 25% of patients with low morbidity. However, since 25% long-term survival and high rates of loco-regional and distant relapse obviously remain unsatisfactory, research opportunities in this specific patient population include the investigation of higher, individualised radiation doses delivered with appropriate conformal techniques to minimise toxicity, improvement in the combination with chemotherapy and possibly even biologically targeted agents as well as consideration of surgery in selected patients [21,24–26].

Conflict of interest notification

None declared.

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