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Quality assurance of thoracic radiotherapy in EORTC 08941: A randomised trial of surgery versus thoracic radiotherapy in patients with stage IIIA non-small-cell lung cancer (NSCLC) after response to induction chemotherapy

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ABSTRACT

The aim of this study was to investigate the improvement of quality of radiotherapy and compliance to the protocol amendment of EORTC study 08941. The radiotherapy-specific data were analysed from 154 patients with stage IIIA-N2 Non-Small-Cell Lung Cancer who were actually irradiated after response to 3 cycles of platinum-based induction chemotherapy. The parameters of quality, assessed in 93 patients before and in 61 after protocol amendment, included: time interval between last chemotherapy course and start of thoracic radiotherapy, the use of a 3-D planning CT, dose and fractionation scheme to the primary tumour, the involved and uninvolved mediastinum, duration of radiotherapy and toxicity. A significant improvement of all quality parameters was noted, except for the overall treatment time, which decreased slightly.

Protocol amendment resulted in an improvement of the quality and the compliance of most observed parameters, at the cost of some increase in overall treatment time. The latter reflects logistical problems rather than poor compliance.

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1. Introduction

Three meta-analyses[1–3] show that the addition of cisplatin containing combination induction chemotherapy followed by radiotherapy results in an absolute survival gain of 4% at 2 years in stage III non-small-cell lung cancer (NSCLC).

In 1994 the European Organisation for Research and Treatment of Cancer (EORTC) Lung Cancer Group launched a randomised trial (08941) in patients with irresectable stage IIIA N2 NSCLC to address the question which locoregional treatment was superior following a response to systemic induction with platinum-based combination chemotherapy: surgical resection or thoracic radiotherapy.[4]

Quality assurance is an important issue in the EORTC.[5] In 1987 the EORTC Radiotherapy Group introduced a series of procedures to document systematic errors, dummy runs, made in single institutions. This dummy run gives information about accuracy of the design and the application of phase III study protocols also. In 1991 Koning[6] recommended immediate monitoring of treatment parameters and uniform assessment of patient data in clinical trials. However, at the start in 1994 of the present randomised study, these quality controls on radiotherapy treatment were not yet implemented. Questions about the quality of radiotherapy data came up halfway the trial, as not all investigators adhered to prescribed treatment schemes. At site visits, the radiotherapy treatment fields and set up appeared to be correct, but compliance to the protocol was subject of improvement.

In May 1999, the protocol was amended with detailing and tightening of the radiotherapy prescriptions. The aim was to improve the quality of and the compliance to the radiotherapy and to enhance the reliability of the final results of the study. This report focuses only on the radiotherapy quality data before and after this protocol amendment.

2. Patients and methods

In EORTC 08941, patients with proven stage IIIA-N2 NSCLC were treated with 3 cycles of platinum-based induction chemotherapy; responding patients were then randomised between thoracic radiotherapy or surgical resection.[7]

The EORTC Protocol Review Committee (PRC) and the local ethical committees approved the protocol and its amendment. All patients had to give informed consent prior to randomisation according to local practice.

In the surgery arm, 165 patients were included and 40% was referred for post-operative radiotherapy because of presumed irradical resection according to the preset definition. These postoperative radiotherapy data are not the subject of this paper.

2.1. *Protocol amendment for improving radiotherapy quality*

In the protocol amendment of May 1999, most of the guidelines for writing protocols published in 1995 by the EORTC Radiotherapy Group[8] were implemented. The protocol was revised with the target volumes redefined according the specifications of the ICRU 50 report.[9] The radiotherapy prescriptions were tightened and updated as follows: planning-CT scan became standard for the whole treatment, timeframes and dose specifications were formulated more precisely, case report forms revised, and radiotherapists instructed (Table 1).

The primary protocol requirements were specified as follows: the primary tumour and areas of radiological nodal involvement had to be treated with at least 2 cm margin to a dose of 60–62.5 Gy using daily fractions of 2 Gy. The lymphatic drainage areas of the uninvolved mediastinum on CT scan of the thorax should have received a dose of 40–45 Gy in daily fractions of 2 Gy. The total radiation dose should have been 60 Gy with lung tissue correction (0.3 or CT-based), given in 30 daily fractions of 2 Gy for 5 treatments per week. The fractionation dose should have been calculated for the target volume and should not have been less than 1.8 Gy. The overall radiotherapy treatment time should not have exceeded 7 weeks. Megavoltage equipment with photon energies of at least 4 MV was required. For fixed Source Skin Distance (SSD) techniques a treatment distance of 100 cm had to be used. In addition to dose distribution in the central axis plane, central dose at upper and lower limits of target volume should have been calculated and wedged filters used as compensators if greater than 10% inhomogeneity resulted from varying tissue thickness. CT–based treatment planning was mandatory for the boost technique only. Treatment could be started with conventional APPA opposed treatment fields. Simulator films and treatment plans with specified target volume and dose distributions had to be available for review.

In the amendment, volumes of interest and organs at risk were more precisely described according ICRU 50 specifications.[9] CT-based 3D-planning with lung tissue correction

Table 1 – Protocol prescriptions before and after the amendment

Before protocol amendment	After protocol amendment
1. CT-based treatment planning mandatory for boost only	1. 3-D planning CT mandatory from start of treatment
2. No time intervals stated for ICT-Rand and Rand-RT	2. Time intervals prescribed (see Table 3)
3. Involved fields: 60–62.5 Gy in 30 fractions	3. Involved fields: 60 Gy in 30 fractions 5x per week
4. Uninvolved regions: 40–45 Gy in 20–23 fractions	4. Uninvolved regions 40–46 Gy in 20–23 fractions 5x per week
5. Fraction size at least 1.8 Gy	5. Fraction size 2.0 Gy
6. Tumour margins $\geqslant$2 cm for involved areas, the margins of the uninvolved areas were not specified.	6. GTV 1 (prechemo involved areas) with $\geqslant$1 cm margin; GTV 2 (uninvolved areas) without margins
	7. Implementation of ICRU 50 guidelines

ICT = induction chemotherapy; RT = thoracic radiotherapy; GTV = gross tumour volume.

became mandatory for the whole radiation treatment. Dose inhomogeneity was accepted between +/− 10%. Dose prescriptions were described more precisely and alternative treatment schemes were no longer allowed.

Minor deviations from the prescribed dose, were defined as tumour dose between 55–66 Gy, dose to the involved mediastinum between 55–66 Gy, and fraction dose between 1.8–2.20 Gy. Major protocol deviations were defined as a fraction size of >2.20 Gy and/or fraction number <28.

2.2. *Data collection on delivered radiotherapy*

The data on the quality of the delivered radiotherapy were retrospectively collected for the period before the introduction of the amendment and prospectively for the period after the amendment. Site visits to participating institutes were performed in 1998 and 1999 by 2 experienced radiation-oncologists of the EORTC Lung Cancer Group. Data checked on site were: field sizes, margins, treatment techniques, and dose delivery.

Toxicity was scored using the National Cancer Institute of Canada Clinical Trials Group Expanded Common Toxicity Criteria.[10] Acute toxicity was scored for white blood cell counts, platelets, upper gastro-intestinal, pharynx and oesophagus, and lung toxicity. Only grade 3–4 toxicities will be discussed in this analysis.

The case report forms were revised according to the new prescriptions. All investigators, and specifically the radiotherapists, were instructed of the changes in protocol guidelines initiated in May 1999. Further, intensification of the data control at the EORTC Data Centre was performed.

2.3. *Endpoints and statistics*

To study the impact of this amendment, we defined a measure of compliance based on: 1) interval scored from the last day of induction chemotherapy (ICT) till the start of thoracic radiotherapy (⩽10 weeks); 2) the use of 3-D planning; 3) the use of lung tissue corrections; 4) the dosages administered to the primary tumour (60–62.5 Gy), the involved – (60–62.5 Gy) and uninvolved (40–46 Gy) mediastinum; 5) the fractionation size (1.95–2.05) and numbers (30–32); and 6) the duration of the radiotherapy treatment (40–46 days). We also report data on the interval between last day of ICT and randomisation, and from randomisation until start of thoracic radiotherapy, as well as toxicity data. Indeed, a reduction in toxicity rate was expected as standard dose prescriptions had to be followed and hypofractionated treatment schemes were not any longer allowed. Descriptive statistics are presented for these variables. All analyses are to be considered as exploratory and unplanned in the protocol.

3. Results

3.1. *Patient inclusion*

EORTC study 08941 accrued 578 patients between December 1994 and December 2002 and of these, 332 were randomised.[7] Among the 165 patients randomised to the radiotherapy arm, 154 patients started their allocated protocol treatment and are the subject of this analysis. Of these, 93 patients were randomised before and 61 after May 1999, period at which the protocol amendment was implemented. A summary of the characteristics of the patients allocated to and actually treated with radiotherapy is given in Table 2. Distribution of gender, T status and histological subtypes are similar between both randomisation periods.

Analysis of portal films and planning data during the site visits revealed no major deviations in target volumes and margins from protocol prescriptions.

3.2. *Compliance to radiotherapy protocol prescription*

Table 3 shows data on compliance to protocol prescriptions for both periods.

Response evaluation after the last chemotherapy course was done within the required time period of 4 weeks or less in 53% of patients before and 72% after the amendment respectively. The number of patients starting thoracic radiotherapy within the required 10 weeks or less after the last induction chemotherapy course, however, decreased from 91% before to 79% after the amendment. The median interval increased from 50 (range 17–113) to 53 (range 20–84) days. There is a trend towards longer time interval after randomisation till thoracic irradiation for patients in The Netherlands than for those patients treated outside The Netherlands (Table 3). Before protocol amendment 11 vs. 4% of the patients was not treated within 6 weeks after randomisation. After protocol amendment this number increased to 29 vs. 12% of the patients, respectively.

Planning-CT was in the initial protocol mandatory for the boost dose only, and after protocol amendment, mandatory from start of the treatment.

All patients were treated with various photon beams of 6–18 MV. The compliance for dose delivery to the primary

Table 2 – Baseline characteristics at registration of patients randomised to the radiotherapy arm

Variable	Randomisation period			
	Before amendment (N = 93)		After amendment (N = 61)	
	N	(%)	N	(%)
Sex				
Male	71	(76)	47	(77)
Female	22	(24)	14	(23)
cT				
T1	10	(11)	10	(16)
T2	68	(73)	42	(69)
T3	14	(15)	9	(15)
Tx	1	(1)	0	(0)
Histological subtype				
Squamous cell	38	(41)	25	(41)
Non-squamous cell	55	(59)	36	(59)
Randomised in The Netherlands				
Yes	66	(71)	53	(87)
No	27	(29)	8	(13)

Table 3 – Overview of compliance to protocol prescription

Protocol prescription		Before amendment	After amendment
		N = 93	N = 61
		Number (%) pts	
Interval	ICT-RT ⩽10 wks	85 (91)	48 (79)
	ICT-Rand ⩽4 wks	49 (53)	44 (72)
	Rand-RT ⩽6 wks	85 (91)	49 (80)
	- in The Netherlands	59 (89)	40 (71)
	- outside The Netherlands	26 (96)	7 (88)
Planning-CT	Performed	82 (88)	59 (97)
	With lung correction	80 (86)	58 (95)
Dose (Gy):	Tumour (60–62.5)	70 (75)	58 (97)
	Mediastinum		
	- Involved (60–62.5)	61 (66)	54 (89)
	- Uninvolved (40–46)	80 (86)	54 (89)
Fraction-numbers	30–32	72 (77)	59 (97)
Fraction size (Gy)	1.95–2.05	75 (81)	59 (97)
Duration	40–46 (days)	67 (72)	56 (92)
Compliance to protocol[a]		45 (48)	40 (66)

ICT = induction chemotherapy; Rand = randomisation; RT = thoracic radiotherapy.
a Includes all items except interval ICT-Rand and Rand-RT.

tumour, the involved and the uninvolved mediastinum, improved from 75 to 97%, 66 to 89% and 86 to 89% respectively.

Overall, the compliance to the protocol improved from 48% (45/93 patients) to 66% (40/61 patients). For all 154 patients, 85 (55%) fulfilled all protocol prescriptions.

Including minor deviations from the prescribed dose, 138 (90%), 125 (81%), and 137 (89%) patients fulfilled the protocol prescriptions respectively. Major deviations were observed in 16 patients (10%), 14 before and 2 after protocol amendment (see Table 4). In 2/16 patients (12%) treatment scheme

Table 4 – Overview of major protocol deviations used in individual patients

Duration (days)	Dose primary (Gy)	Fraction numbers	Fraction dose	BED tumour	BED for late toxicity
Before protocol amendment					
23[a]	35.0	16	2.18	[a]	[a]
40	56.0	24	2.33	69.0	121
34	55	22	2.50	62.5	124
43	48.0	18	2.66	60.8	112
22	48.0	16	3.00	62.4	120
22	45.0	15	3.00	58.5	112
22	45.0	15	3.00	58.5	112
22	45.0	15	3.00	52.2	112
21	45.0	15	3.00	58.5	112
22	45.0	15	3.00	58.5	112
22	45.0	15	3.00	58.5	112
22	45.0	15	3.00	58.5	112
15	40	8	5.00	72	200
16	40.0	8	5.00	72	200
After protocol amendment					
31[a]	45.0	20	2.25	[a]	[a]
39	56.0	23	2.43	69.6	124
Prescribed dose					
40	60.0	30	2.00	72	120

Formula for reference treatment:
$BED_{ref} = Dose_{ref}\ [1 + \text{fraction dose}_{ref}/(\alpha/\beta)]$.
α/β for tumour = 10, and for late toxicity $\alpha/\beta = 2$.
a Patients stopped because of distant metastasis.

was changed because distant metastasis occurred during radiotherapy treatment.

3.3. *Toxicity of radiotherapy*

The Biological Effective Dose (BED) for tumour and late toxicity is given (Table 4) for the aberrant treatment schemes. Only 5 (5%) patients before the amendment and 2 (3%) patients after the protocol amendment had toxicity grade 3–4 in any of these variables (Table 5). Two patients with pre-existent lung fibrosis died because of a radiation pneumonitis after induction chemotherapy with gemcitabine/cisplatin.

4. Discussion

In 1999, quality control of EORTC 08941 showed limited protocol compliance mainly due to the use of hypofractionated treatment schemes. That was the reason for a protocol amendment with more strict prescriptions on the radiotherapy delivery. We observed that due to this amendment, overall treatment parameters as dose, fractionation, and overall treatment time substantially improved. The stricter regulations in the amendment resulted in a gain in overall compliance to the protocol of 17%.

Unexpectedly, we also observed that despite the more strict protocol prescription, the proportion of patients starting with radiotherapy within 10 weeks of the last cycle of chemotherapy actually declined from 91% to 79%. This was mainly due to an increased delay between randomisation and start of radiotherapy and not due to a further delay between chemotherapy and randomisation. Apparently, chest physicians and medical oncologists became now also aware of the importance to improve their time schedule. The use of a planning-CT, which became mandatory for the whole treatment course, was probably the main reason the number of patients started with thoracic radiotherapy within 10 weeks after finishing chemotherapy decreased. Planning-CT is a more time-consuming technique than conventional simulation.[11] Furthermore, a shortage of radiation equipment[12] could be responsible for the lengthening of the time interval, as a large majority (77%) of the patients in this study were treated in the Netherlands (Tables 2 and 3). However, we consider the gain in quality control with the introduction of a planning-CT for the whole treatment to be more important on the main outcomes of this trial than the increase of 3 days of the median time before and after the amendment.

The Planning Target Volume (PTV) prescribed by the protocol amendment, had a margin of $\geqslant 1$ cm around the pre-chemotherapy tumour areas and pathological hilar or mediastinal nodes (Gross Tumour Volume or GTV). All patients in this study had at least a response at randomisation.

Shih[13] showed for fast CT-scan at shallow free breathing that internal margins (expansion margins) of 13 mm are required to approximate the composite GTV in 95% of cases. Van Sörnsen de Koste[14] showed that margins of 15 mm around GTV in immobile tumours using conventional

Table 5 – Acute toxicity in thoracic radiotherapy after induction chemotherapy

Variable	Randomisation period			
	Before protocol amendment (N = 93)		After protocol amendment (N = 61)	
WBC (10^9/l)				
⩾4	69	(74)	46	(75)
2–<4	8	(9)	4	(7)
<2	0		0	
unknown/missing	16	(17)	11	(18)
Platelets (10^9/l)				
⩾100	39	(42)	48	(79)
50–<100	1	(1)	1	(2)
<50	1	(1)	0	(0)
unknown/missing	52	(56)	12	(20)
Upper GI toxicity				
Degree 0	59	(63)	42	(69)
Degree 1–2	34	(37)	19	(31)
Degree 3–4	0		0	
Pharynx and Oesophagus toxicity				
Degree 0	19	(20)	15	(25)
Degree 1–2	74	(80)	45	(74)
Degree 3–4	0		1	(2)
Lung toxicity				
Degree 0	46	(50)	26	(43)
Degree 1–2	42	(45)	34	(56)
Degree 3–4	4	(4)	1	(2)
Missing	1	(1)	0	
Other acute toxicity				
No	80	(86)	49	(80)
Yes	13	(14)	12	(20)

planning-CT are adequate, but in mobile tumours the coverage is still inadequate in 11% of the cases. Lagerwaard[15] recently showed in reconstructing pre-chemotherapy target volumes clinicians may fail to treat the actual pre-chemotherapy tumour volume in 26% of the cases. This can result in lower local control, but no data exist of randomised trials in treating pre- or post-chemotherapy target volumes. Therefore, we consider the margin of $\geqslant 1$ cm around prechemotherapy tumour areas and mediastinal nodes used in the present protocol as adequate. The majority of patients were planned using a 3-D planning-CT during this study, reaching 99% after protocol amendment. Thus, based on the above mentioned findings and the pre-amendment site visits, we believe that no major concerns exist about the quality of and the compliance to treatment planning volumes.

Before protocol amendment, a major protocol violation in the administered tumour dose was present in 15% of patients with doses to primary tumour of less than 55 Gy or in excess of 66 Gy. These findings were worse than found in an earlier study wherein incorrectly given radiation doses were reported in only 7% of the cases.[6] Although the protocol already recommended fraction doses of 1.8–2.0 Gy at initiation of the study, capacity problems in several hospitals led to the introduction of hypofractionated treatment schemes. After amendment of the protocol, it was stressed that dose prescriptions had to be strictly followed. This resulted in a substantial improvement of the protocol compliance. A reduction in overall treatment time to 20–24 days using hypofractionated schemes on locoregional control is evident. Lester[16] treated stage I–III NSCLC patients to 50–55 Gy in 15–20 fractions over 3–4 weeks. This resulted in a favourable outcome compared to standard radical radiotherapy data. Cheung[17] used 48 Gy in 12 once-daily fractions for early stage non-small-cell lung cancer patients with a recurrence free survival after 2 years of 40%. The CHART study[18] showed a reduction of overall treatment time to 12 consecutive days with a hyperfractionated treatment scheme of thirty-six fractions of 1.5 Gy given three times per day, resulting in a gain in two-year survival of 9%, compared to 30 fractions of 2 Gy to a total dose of 60 Gy in 6 weeks.

On the other hand, hypofractionation can increase the risk of late toxicity. Abratt[19] showed that the biological effect of radiation on tumours is increased as overall treatment time is shortened, but this is not true for late-reacting normal tissue. However, for patients with stage III tumours treated with combined modality more conservative hypofractionation regimens are warranted. The BED for late toxicity in only 2 hypofractionation schemes (BED 200) is much higher than in the standard treatment scheme (BED 120).[20] Therefore, no differences in toxicity over both periods were to be expected.

The two patients, who died after induction chemotherapy followed by radiotherapy, were both treated according to the initial protocol prescriptions, but suffered from interstitial lung fibrosis.[21] Maas[22] showed the combination of gemcitabine/cisplatin as part of combined modality treatment, especially radiotherapy, resulted in a decline of pulmonary function and could be responsible for an increase of toxicity. However, van Zandwijk[21] showed that the combination of gemcitabine/cisplatin is safe as induction treatment. Therefore, patients with interstitial lung fibrosis were hence excluded from further inclusion in 08941.

This trial was running over a period of more than 8 years. During this period, radiotherapy techniques changed to the actual standards. The progress in simulation techniques urged for standard 3-D planning techniques. The improvement of protocol compliance after the amendment supports the earlier recommendation of immediate monitoring of treatment parameters and uniform assessment of patient data in clinical trials. For future trials we would recommend routine checks on the quality of (any) delivered treatment as this would provide the possibility of corrections in the protocol shortly after start of a study and guarantee compliance.

In conclusion, after protocol amendment, a substantial improvement to protocol compliance was observed, despite some increase in overall treatment time. The latter is thought to reflect logistical problems rather than poor compliance. The use of hypofractionated treatment schemes is of some concern with respect to the outcome of the trial. Our data support the use of strict radiotherapy specifications, dummy runs, and quality control from the start of a large study and frequent quality assessments during it.

Conflict of interest statement

None declared

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