Radiotherapy and Oncology 115 (2015) 3–8

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Lung cancer

An instrument dedicated for modelling of pulmonary radiotherapy

Anne G.H. Niezink [a,*], Nienke J. Dollekamp [a], Harriet J. Elzinga [a], Denise Borger [a], Eduard J.H. Boer [a], Jan F. Ubbels [a], Marleen Woltman-van Iersel [a], Annija H.D. van der Leest [a], Max Beijert [a], Harry J.M. Groen [b], Jan Kraan [b], Thijo J.N. Hiltermann [b], Anthonie J. van der Wekken [b], John W.G. van Putten [c], Steven R. Rutgers [d], Remge M. Pieterman [e,f], Sander M. de Hosson [g], Anke W.J. Roenhorst [h], Johannes A. Langendijk [a], Joachim Widder [a]

[a] Department of Radiation Oncology; [b] Department of Pulmonary Diseases, University of Groningen, University Medical Center Groningen; [c] Martini Hospital, Groningen; [d] Scheper Hospital, Emmen; [e] Ommelander Hospital Group, Delfzijl; [f] Ommelander Hospital Group, Winschoten; [g] Wilhelmina Hospital, Assen; and [h] Refaja Hospital, Stadskanaal, The Netherlands

ARTICLE INFO

Article history:
Received 3 December 2014
Received in revised form 6 March 2015
Accepted 15 March 2015
Available online 9 April 2015

Keywords:
Lung cancer
Thoracic radiotherapy
Patient-rated outcome measures

ABSTRACT

Background and purpose: Radiotherapy plays a pivotal role in lung cancer treatment. Selection of patients for new (radio)therapeutic options aiming at improving outcomes requires reliable and validated prediction models. We present the implementation of a prospective platform for evaluation and development of lung radiotherapy (proPED-LUNG) as an instrument enabling multidimensional predictive modelling.

Materials and methods: ProPED-LUNG was designed to comprise relevant baseline and follow up data of patients receiving pulmonary radiotherapy with curative intent. Patient characteristics, diagnostic and staging information, treatment parameters including full dose–volume-histograms, tumour control, survival, and toxicity are scored. Besides physician-rated data, a range of patient-rated data regarding symptoms and health-related quality-of-life are collected.

Results: After 18 months of accrual, 315 patients have been included (accrual rate, 18 per month). Of the first hundred patients included, 70 received conformal (chemo)radiotherapy and 30 underwent stereotactic radiotherapy. Compliance at 3 and 6 months follow-up was 96–100% for patient-rated, and 81–94% for physician-rated assessments. For data collection, 0.4 FTE were allocated in a 183 FTE department (0.2%).

Conclusions: ProPED-LUNG is feasible with high compliance rates and yields a large amount of high quality prospective disease-related, treatment-related, patient- and physician-rated data which can be used to evaluate new developments in pulmonary radiotherapy.

Both conformal radiotherapy with or without chemotherapy and stereotactic ablative radiotherapy (SABR) play important roles in the treatment of early and locally advanced stages of non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) as well as in the treatment of pulmonary oligometastases [1,2]. The absolute level and distribution of radiation dose in target volumes and organs at risk (OAR's) are the most critical modifiable parameters that determine the optimal balance between tumour control and toxicity. Indirectly, these parameters influence quality of life during and after radiotherapy and survival. Besides modifying overall treatment time and fractionation, the progress of radiotherapy during the past decades has mainly focused on improving dose-conformity, increasing the dose to the tumour, and reducing exposure of OAR's [3,4].

Non-surgical treatment of early stage NSCLC has been considerably advanced by the introduction of SABR by dramatically increasing the dose per fraction together with improving targeting precision using 4D-planning and image guidance of treatment delivery [5]. For locally advanced NSCLC and SCLC, concurrent chemoradiotherapy has become the standard therapy [6,7], including improvements in dose distribution by using intensity modulation and inverse planning [8]. Using protons instead of photons in this setting is expected to further improve the therapeutic ratio in selected patients [9]. The selection process of these patients will require models predicting the additional gain when using this new technology [10].

Valid data on patient-rated symptoms and health-related quality-of-life (HR-QOL) can only be collected prospectively [11]. Any retrospective assessment of toxicity or other qualitative

* Corresponding author at: Department of Radiation Oncology, University Medical Center Groningen, PO BOX 30001, 9300 RB Groningen, The Netherlands.
E-mail address: a.g.h.niezink@umcg.nl (A.G.H. Niezink).

http://dx.doi.org/10.1016/j.radonc.2015.03.020
0167-8140/

measure is subject to inevitable bias. In addition, imaging and other functional assessments (e.g., pulmonary function tests) need to be gathered prospectively. For these reasons and building on the experience gained with a prospective SABR database at our department, we developed and clinically implemented a prospective platform for evaluation and development of lung radiotherapy (proPED-LUNG) in February 2013. By establishing a comprehensive database of all patients receiving high-dose radiotherapy (i.e., >40 Gy, any fractionation) for lung cancer, pulmonary oligometastases or thymic tumours, the main purpose of this prospective data registration programme is to enable modelling of all clinically relevant endpoints of pulmonary radiotherapy. By modelling relevant outcomes including tumour control, survival, toxicity, patient-rated adverse events and HR-QOL, this instrument aims at improving the quality of pulmonary radiotherapy by predicting effects of modification of critical treatment parameters such as dose–volume-distributions. The platform is designed in such a way that other institutions could easily adopt it, which is fundamental for pooling and exchange of data [12].

To our knowledge, this is the first comprehensive programme operating fully integrated into daily clinical practice of radiotherapy. The aim of this paper was to describe the programme contents, patient accrual, compliance, and its feasibility based on our experience during the first 18 months. We also present the basic results of the first 100 patients included.

Materials and methods

Background and programme design

Treatment within a multidisciplinary pulmonary oncology team is considered standard for lung cancer patients in the Netherlands. Questionnaires and items included in proPED-LUNG were selected by a group of experienced radiation oncologists specialised in pulmonary oncology. The programme was discussed with pulmonary oncologists, who are the primary treating physicians for patients with lung cancer in this country. They coordinate the diagnostic process, perform necessary endoscopies and biopsies, and administer systemic treatment including chemotherapy and biologically targeted agents. In addition, they follow-up patients according to national guidelines. ProPED-LUNG was presented to the hospital's institutional review board and was declared exempt from ethics committee approval being standard patient management according to Dutch law. All information used and generated for proPED-LUNG is entered real-time into the patient chart in our oncology management system (OMS, Mosaiq®, IMPAC Medical Systems, Inc. Sunnyvale, California U.S.A.). All data are presently stored in the OMS, which is protected by hospital firewalls and safety rules. For future analysis, data will be pseudonymised twice (by a trusted third party) and stored on a secure server where they can be used for analysis in protected workspaces by authorised persons. Imaging is uploaded into our hospital picture archiving and communication system (PACS). Automatic and semi-automatic quality and plausibility checks are performed before analysis of the data.

Patient eligibility, assessment, and data acquisition

All patients receiving high-dose radiotherapy (defined as >40 Gy using any fractionation schedule) for lung cancer or thymic tumours without simultaneous second non-pulmonary tumours and able to understand and speak Dutch are eligible on a day-by-day basis regardless of treatment techniques employed, SABR-VMAT, 3D-CRT, IMRT, or VMAT. Data covering all clinically relevant dimensions of pulmonary radiotherapy are collected prospectively, including baseline patient characteristics, diagnostic and staging information, pulmonary function tests, treatment parameters, and outcome in terms of survival, tumour control, disease-related symptoms (including pulmonary complaints, use of corticosteroids, performance status) and treatment related side effects (including pulmonary-, oesophageal-, and skin toxicity and unplanned hospitalisations during or after treatment). The latter two domains are rated by patients as well as by physicians. Appendix A1 shows the assessments and questionnaires as used.

The programme aims at its feasibility in daily clinical routine at a radiotherapy department including its satellite location (for radiotherapy) plus seven referring departments of pulmonology. Patient characteristics include usual demographic data. Diagnostic and staging information is retrieved from standard clinical investigations. All patients undergo a diagnostic 18F-fluorodeoxyglucose-positron emission tomography and computed tomography (FDG-PET/CT), pulmonary function tests, and biopsies whenever possible. Pulmonary function tests at baseline and at three months after treatment include forced expiratory volume in 1 s (FEV1, expressed as percentage of expected) and diffusing capacity of carbon monoxide for a single breath, corrected for haemoglobin concentration (DLCOc/SB, expressed as percentage of expected). Radiotherapy treatment parameters consist of start and end date of radiation therapy, number of fractions, fraction dose, technique used, and dose–volume-histograms for target volumes and OAR's (e.g., lung, oesophagus, heart, spinal cord). Chemotherapy received prior to or during radiotherapy is also recorded.

Tumour control and survival status including recurrence patterns and causes-of-death are collected real-time and are based on imaging and on correspondence from pulmonary oncologists.

Disease-related symptoms and treatment related side effects are scored both by patients (patient-rated data) and radiation oncologists (physician-rated data). Patient-rated data are acquired face-to-face at baseline and during treatment by trained research assistants using the following questionnaires (Appendix A1): EuroQOL-5D, EORTC-QLQ-LC13-short (LC13 excluding the questions referring to sore tongue or mouth, tingling hands or feet, and hair loss and the pain-in-other-parts-of-the-body question), and the Groningen Frailty Indicator (GFI) [13]. The latter instrument was chosen because frailty relates more to a decline in self-management abilities than does chronological age [14]. The GFI is a short and easy-to-use 15-item screening instrument assessing loss of functions and resources in four domains of functioning: physical, cognitive, social, and psychological [13,14]. In addition, a structured self-developed questionnaire to assess critical CTCAEv4.0-based toxicity items is also used (Appendix A1). The same instruments are administered by the research assistants during follow-up by telephone to increase compliance and to spare patients extra visits to the department of radiotherapy (proxy-based-assessments). In support of this approach, a recent randomised trial investigating face-to-face versus telephone interviews for HR-QOL and symptom assessments in COPD patients has shown equal results for both approaches [15].

Physician-rated data consist of a baseline assessment by the treating radiation oncologist including the WHO-performance status, weight loss three months before diagnosis, and again a CTCAEv4.0-based toxicity assessment. This toxicity assessment is also used during radiotherapy for weekly monitoring of side effects and shortly after the end of radiotherapy (2–4 weeks). To assess oesophageal and pulmonary toxicity at follow-up, imaging and written correspondence from pulmonary oncologists is scored prospectively by a radiation oncologist-researcher in order to avoid duplication of patient visits to the hospital. The frequencies of patient- and physician-rated assessments are displayed in Table 1.

Table 1
ProPED-LUNG overview assessments.

Executive	Assessment	Baseline	During radiotherapy		After radiotherapy		
			Weekly	Last week	3 months	6 months	Yearly
Research assistant	EuroQOL-5D	+		+	+	+	+
	EORTC-LC13-short	+		+	+	+	+
	Toxicity assessment CTCAE v 4.0	+		+	+	+	+
	Groningen frailty index	+					
Pulmonary oncologists	Pulmonary function tests*	+			+		
	Imaging**	+			+	+	+
	Correspondence of patient visits**	+			+	+	+
Radiation oncologists	Baseline assessment	+					
	Toxicity assessment CTCAE v 4.0	+	+				
Researcher/radiation oncologists	Tumour assessment				+	+	+
	Toxicity assessment CTCAE v 4.0				+	+	+

Abbreviations: ProPED-LUNG, prospective platform for evaluation and development of lung radiotherapy; EORTC-LC13-short, short version of the EORTC-QLQ-LC13 including radiotherapy relevant toxicity only; *forced Expiratory Volume in one second (FEV1) in % of expected and single-breath diffusing capacity of the lung for carbon monoxide DLCO (sb) in % of expected and corrected for haemoglobin. **Imaging (including computed tomography and X-ray) and correspondence of visits to the outpatient clinic according to the national guidelines.

Table 2
Patient characteristics and tumour characteristics.

Characteristic		Total (n = 100/103*)	Conformal radiotherapy (n = 70) No. (%)	Stereotactic radiotherapy (n = 30/33*) No. (%)
Age (years)	Median (Range)	67 (45–86)	65 (45–80)	72 (54–86)
Sex	Male	53	38 (54%)	15 (50%)
	Female	47	32 (46%)	15 (50%)
WHO performance status	0	35	26 (37%)	9 (30%)
	1	43	31 (44%)	12 (40%)
	2	17	9 (13%)	8 (27%)
	3	5	4 (6%)	1 (3%)
GFI	<4 (non-frail)	56	41 (59%)	15 (50%)
	⩾4 (frail)	41	26 (37%)	15 (50%)
	Missing	3	3 (4%)	0 (0%)
Tumour type	NSCLC	60	54 (77%)	6 (18%)
	SCLC	9	9 (13%)	0 (0%)
	Pathology unknown	21	3 (4%)	18 (55%)
	Recurrence	3	3 (4%)	0 (0%)
	Pulmonary metastases	10	1 (1%)	9 (27%)
Stage (UICC)	IA	15	0 (0%)	15 (45%)
	IB	8	1 (1%)	7 (21%)
	IIA	3	2 (3%)	1 (3%)
	IIB	5	4 (6%)	1 (3%)
	IIIA	34	34 (49%)	0 (0%)
	IIIB	22	22 (31%)	0 (0%)
	IV	16	7 (10%)**	9 (27%)

Abbreviations: GFI, groningen frailty index; UICC, Union for International Cancer Control; *in 100 patients, 103 tumours were treated; **four patients with synchronous brain metastases, one with a second contralateral lung lesion, one with a long metastasis from rectal carcinoma treated with conformal radiotherapy after irradical resection, and one with a suspicious rib lesion.

Treatment schedules

At our department, medically inoperable patients with early stage NSCLC without nodal disease receive SABR. Four risk-adapted fractionation schedules are currently used: three fractions of 18 Gy for peripheral lesions, five fractions of 12 Gy for lesions adjacent to the thoracic wall, eight fractions of 7.5 Gy for central lesions not abutting the main bronchi, and twelve times 5 Gy, if the PTV encompasses a main bronchus [16]. SABR is also applied for pulmonary oligometastases using the same fractionation schedules [2].

Patients with inoperable stage III NSCLC are treated with concomitant chemoradiotherapy, consisting of two cycles of induction chemotherapy (cisplatin/pemetrexed for non-squamous histology, cisplatin/gemcitabine for squamous subtypes) followed by radiotherapy, consisting of 60 Gy in daily fractions of 2.4 Gy combined with weekly low-dose gemcitabine [17]. For limited-disease-SCLC, four cycles of chemotherapy (cisplatin/etoposide) are combined with radiotherapy. Thoracic radiotherapy starts at the second cycle and is typically given twice a day to 45 Gy in fractions of 1.5 Gy [18]. After finishing the fourth chemotherapy cycle, prophylactic cranial irradiation is given to 25 Gy in fractions of 2.5 Gy, four times a week [19,20].

All thoracic treatments are planned using 4D-planning-CT. An internal target volume (ITV) is delineated encompassing the envelope of the moving gross target volume locations (GTV's) on a maximum intensity projection reconstruction from the 4D-CT. For SABR-VMAT, an isotropic margin of 5 mm is added to the ITV to create the planning target volume (PTV). For patients receiving conformal radiotherapy, FDG-PET positive tumour and lymph nodes are defined as GTV, assisted by deformable image

Table 3
Compliance rates of the first hundred patients included in proPED-LUNG.

	Item	Baseline (n = 100)	3 months (n = 99)	6 months (n = 87)
Patient-rated data	EuroQOL-5D	94%	96%	100%
	EORTC-LC13-short	97%	96%	100%
	Groningen frailty index	97%	x	x
	Toxicity (based on CTCAEv4.0)	100%	99%	99%
Physician-rated data	Toxicity assessment	94%	81%	89%
	Tumour assessment	x	83%	94%
Pulmonary function*	FEV1	93%	72%	x
	DLCO	64%	49%	x

Abbreviations: ProPED-LUNG, prospective platform for evaluation and development of lung radiotherapy; EORTC-LC13-short, short version of the EORTC-QLQ-LC13 including radiotherapy relevant toxicity only; *forced expiratory volume in one second (FEV1) in % of expected and single-breath diffusing capacity of the lung for carbon monoxide DLCO (sb) in % of expected and corrected for haemoglobin.

registration of PET and diagnostic CT images. The ITV is delineated as described. A margin of 5 mm is added for clinical target volume (CTV) excluding bony structures and an additional margin of 6 mm is added for the PTV. Verification is performed with 3D- or 4D-cone-beam-CT (CBCT) or with electronic portal imaging devices (EPID) at least weekly for CRT, and online at every fraction for SABR, employing standardised institutional decision rules.

Results

Patient and tumour characteristics

The programme was opened in February 2013 and until July 2014 (18 months), 315 patients were eligible and actually included in proPED-LUNG (on average: 18 patients/month). No patient refused to be included. To show the feasibility of the platform, data of the first hundred included patients – because they had completed at least 6 months follow-up – are presented. One hundred and three tumours were treated in the first 100 patients. Based on tumour volume, patients were divided in two main groups for this report: The SABR-group (n = 30), including patients with early stage NSCLC or those with pulmonary oligometastases, and the conformal radiotherapy (CRT) group (n = 70), including patients with locally advanced NSCLC or SCLC who were treated with conventionally planned 3D-CRT, IMRT, or VMAT, mostly combined with chemotherapy. Patient and tumour characteristics are listed in Table 2.

Compliance and implementation of proPED-LUNG

For the first 100 patients, patient-rated baseline and follow up questionnaires were completed in more than 90% of the cases; physician-rated baseline and follow up data were available in more than 80% of the cases (Table 3). The research assistants spend 14 h on average per week on data collection, corresponding to 0.4 full-time equivalents in a 183 FTE department (0.2% of total FTEs).

Toxicity

First preliminary results regarding the two most important side effects of pulmonary radiotherapy are briefly presented here. Pneumonitis CTCAE v 4.0 grade $\geqslant$ 2 requiring medical intervention (e.g., steroid treatment), was seen in 10% of the patients treated with CRT within 6 months after radiotherapy (none after SABR). Grading of oesophageal toxicity for patients receiving conformal (chemo) radiotherapy is presented in Fig. 1, where three patient-rated and one physician-rated assessment are displayed, comparing the prevalence of events at every time point. Most oesophageal toxicity was observed in the CRT-group at the end of radiotherapy, as expected. Forty-four percent of the patients had at least quite a bit trouble swallowing as assessed by EORTC-QLQ-LC13, which is consistent with patient-rated CTCAE-based dysphagia grade $\geqslant$ 1 (symptomatic, able to eat regular diet), which also yielded 44% (Appendix A1). CTCAE-based patient-rated dysphagia grade $\geqslant$ 2 (requiring change of diet) was scored by 24%. Patient-rated grade $\geqslant$ 2 CTCAE-based oesophageal pain was scored in 41% of the cases. Physician-rated grade $\geqslant$ 2 oesophageal toxicity representing pain swallowing in the first place was scored for 45% of the patients, suggesting very reasonable agreement between patient-rated (proxy assessed) and physician-rated assessment of acute oesophageal toxicity.

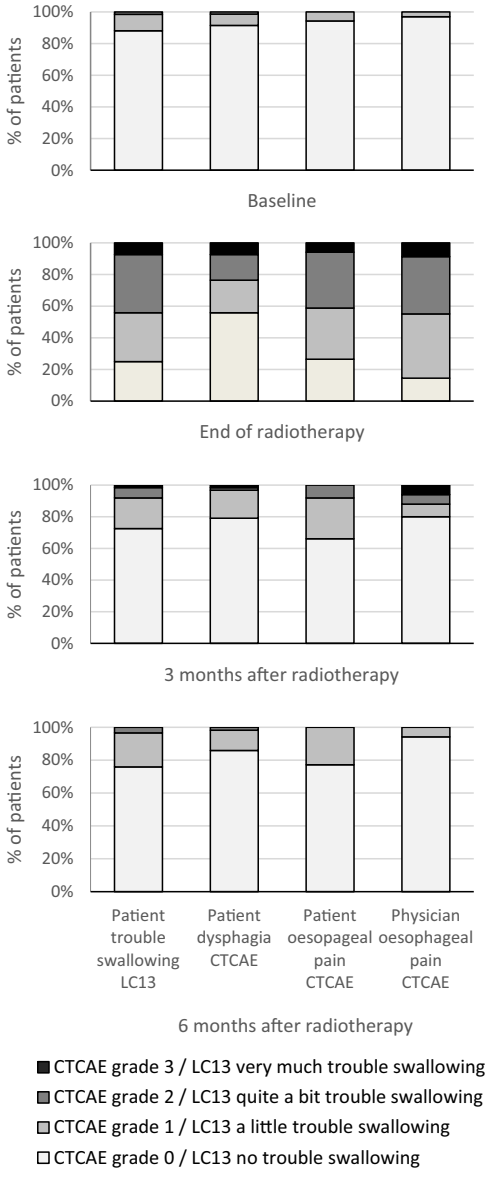

Fig. 1. Oesophageal toxicity for patients treated with conformal (chemo) radiotherapy. CTCAE: CTCAE v4.0; LC13: EORTC-QLQ-LC13.

Quality of life

To show an example of a quality of life outcome, the EQ-5D health status was converted into a single summary index as

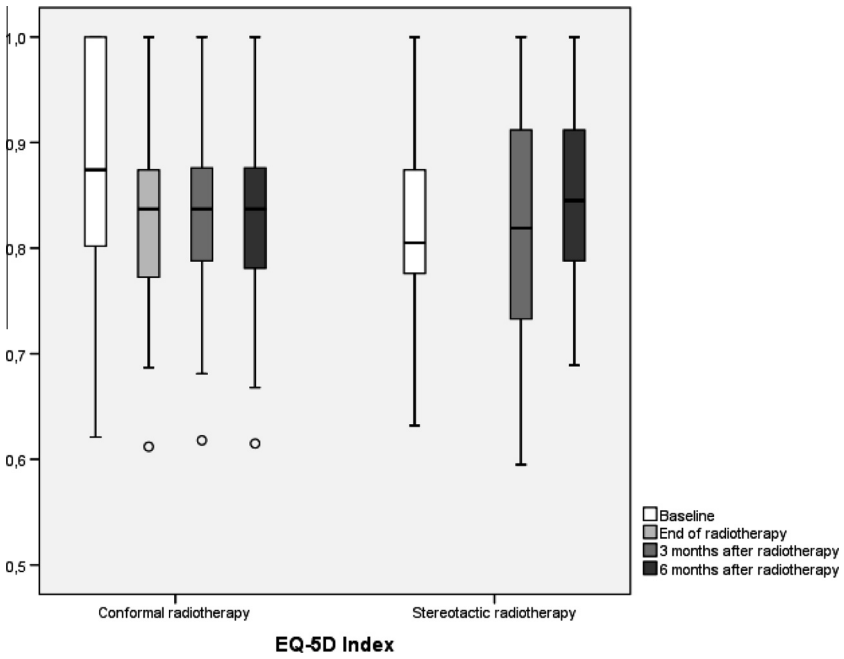

Fig. 2. Boxplot of the EQ-5D index values at different time points for patients treated with conformal radiotherapy and stereotactic radiotherapy. The dots represent outliers.

appropriate, using the time trade-off valuation technique as available for the Netherlands. In Fig. 2 the values are presented for CRT and SABR for assessed points in time.

Dose–volume histograms

Dose–volume histograms were available for all patients. In the CRT-group, median and range for the V5 and V20 of the lung were 54% (range 23–79%) and 23% (range 10–34%), respectively. The median mean lung dose (MLD) was 13% (range 1–18%). Median V35 of the oesophagus was 33% (range 0–72%). In the SABR-group, median V20 of the lungs was 5.1% (range 1.2–15.3%) and the median MLD was 4.5% (range 1.3–10.5%).

Survival

At a median follow up of 11 months, overall survival (OS) after 6 and 12 months in the CRT-group was 83% and 71%, progression free survival (PFS) was 66% and 41%, respectively. For the SABR-group, OS was 97% after 6 months and 92% after 12 months; PFS was 83% and 60%, respectively. Of note, 27% of the patients in the SABR-group were treated for oligometastases, explaining the considerable progression-rate at one year [2].

Due to the limited number of patients and short follow up, patterns of recurrence were not analysed.

Discussion

In this paper, we report successful implementation into clinical practice of a standardised programme of prospective data acquisition for patients receiving definitive radiotherapy for primary or secondary lung lesions. Radiation technique is rapidly changing, and typically, progress is obtained in multiple small steps. This continuous improvement, from version to version, using feedback from daily use contains the same steps as frequently used in quality management, resulting in a plan-do-check-act cycle (PDCA cycle) [21]. Management tools and classical randomised comparative clinical trials (RCT's) should be supplemented by research producing and testing prediction models, which require quality as well as quantity of relevant data [22]. It should be emphasised that proPED-LUNG was not set up with the aim to test a specific hypothesis, but rather to provide a platform upon which modelling of any relevant dimensions of (combined) radiotherapy of intrathoracic malignancies will be made feasible, using prospectively collected data with high compliance in order to improve the generalisability of the multivariable prediction models derived from this programme. This programme, integrating a broad range of radiotherapy research data types, is fully compatible with and can actually be viewed as an important element in a robust and usable radiotherapy exchange strategy such as recently presented by Skripcak et al. [12]. Adopting our platform will enable data exchange and pooling.

ProPED-LUNG yields an enormous amount of information with relatively little resource investment (0,4 FTE for 18 new patients/month). It should be noted that this is only achievable in a setting in which all disciplines work closely together in well organised care pathways. An important part of the programme is the integration of patient-rated symptoms and outcome measures (PROM's). Others have used such tools, but both the combination with other clinically relevant data and feasibility in a busy department with a considerably better compliance, as shown in the present paper, is the strength of proPED-LUNG [23]. Due to notorious difficulties with compliance and completeness of self-assessment by patients on paper (EORTC-QLQ-C30 and LC13) during our first 700 patients receiving SABR, we decided to use a proxy-based system where trained research assistants complete the questionnaires with the patient, asking the relevant questions and securing completeness. High compliance attained already for the first 100 patients seems to support this decision (Table 2). ProPED-LUNG presented in this paper is in accordance with most of the recommendations concerning selection of measures and implementation methods [11] as far as it contains a number of patient-rated outcomes which are considered appropriate for the patient population and as far as it includes a HR-QOL assessment enabling cost-utility analyses. We have taken considerable effort to limit the amount of data collected so that patients can complete the questions within 20 min or less. Although internal and external validation of the programme is still pending, the results regarding oesophageal toxicity

(Fig. 1) suggest a high rate of agreement between patient- and physician-rated assessments and between different questionnaires measuring various intensities of toxicities (e.g., EORTC-LC13 difficulty swallowing is – due to the wording – more sensitive for dysphagia taken literally, while patient and physician-rated pain swallowing nicely correspond with each other, Appendix A1). In a recent randomised trial comparing face-to-face interviews with telephone interviews for a COPD assessment test, the authors concluded that both modes yield valid and reliable data [15].

The results presented here are only the starting point demonstrating the feasibility of the programme. After inclusion of more patients and sufficient follow-up time, the following steps will be to perform additional analyses combining PROM's, physician-reported outcomes measures, imaging data, and DVH data, in order to develop multivariable prediction models of different clinically relevant endpoints using advanced statistical techniques [24,25]. Using this prospective database it is also possible at any time to draw training and validation sets for numerous outcome parameters, which will lead to dynamically adapted models reflecting clinical reality. Any advancement in treatment technology, such as perfecting volumetric modulated arc therapy, changing the combined systemic component (chemotherapy) of the treatment, or the introduction of scanning-beam proton therapy, can be evaluated and adapted almost real-time.

Conclusion

Prospective data collection and analysis are essential to underpin new developments in the field of radiotherapy and will help to improve treatment outcome of lung cancer. ProPED-LUNG is a feasible tool achieving high compliance, which can be easily integrated into daily clinical routine and could be implemented in principle at any department treating patients with intrathoracic tumours with computer-based treatment plans.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2015.03.020.

References

[1] Johnson DH, Schiller JH, Bunn Jr PA. Recent clinical advances in lung cancer management. J Clin Oncol 2014;32:973–82.

[2] Widder J, Klinkenberg TJ, Ubbels JF, Wiegman EM, Groen HJ, Langendijk JA. Pulmonary oligometastases: metastasectomy or stereotactic ablative radiotherapy? Radiother Oncol 2013;107:409–13.

[3] Widder J. The origins of radiotherapy: Discovery of biological effects of X-rays by Freund in 1897, Kienbock's crucial experiments in 1900, and still it is the dose. Radiother Oncol 2014.

[4] Partridge M, Ramos M, Sardaro A, Brada M. Dose escalation for non-small cell lung cancer: analysis and modelling of published literature. Radiother Oncol 2011;99:6–11.

[5] Solda F, Lodge M, Ashley S, Whitington A, Goldstraw P, Brada M. Stereotactic radiotherapy (SABR) for the treatment of primary non-small cell lung cancer; systematic review and comparison with a surgical cohort. Radiother Oncol 2013;109:1–7.

[6] Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 2010;28:2181–90.

[7] Fruh M, De Ruysscher D, Popat S, et al. Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24:vi99–vi105.

[8] Harris JP, Murphy JD, Hanlon AL, Le QT, Loo Jr BW, Diehn M. A population-based comparative effectiveness study of radiation therapy techniques in stage III non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2014;88:872–84.

[9] Chang JY, Komaki R, Lu C, et al. Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III nonsmall cell lung cancer. Cancer 2011;117:4707–13.

[10] Langendijk JA, Lambin P, De Ruysscher D, Widder J, Bos M, Verheij M. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. Radiother Oncol 2013;107:267–73.

[11] Basch E, Abernethy AP, Mullins CD, et al. Recommendations for incorporating patient-reported outcomes into clinical comparative effectiveness research in adult oncology. J Clin Oncol 2012;30:4249–55.

[12] Skripcak T, Belka C, Bosch W, et al. Creating a data exchange strategy for radiotherapy research: towards federated databases and anonymised public datasets. Radiother Oncol 2014;113:303–9.

[13] Schuurmans H, Steverink N, Lindenberg S, Frieswijk N, Slaets JP. Old or frail: what tells us more? J Gerontol A Biol Sci Med Sci 2004;59:M962–5.

[14] Hamaker ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, van Munster BC. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. Lancet Oncol 2012;13:e437–44.

[15] da Silva GF, Morano MT, Sales MP, Olegario NB, Cavalcante AG, Pereira ED. Comparison of face-to-face interview and telephone interview administration of COPD assessment test: a randomized study. Qual Life Res 2014;23:1193–7.

[16] Widder J, Postmus D, Ubbels JF, Wiegman EM, Langendijk JA. Survival and quality of life after stereotactic or 3D-conformal radiotherapy for inoperable early-stage lung cancer. Int J Radiat Oncol Biol Phys 2011;81:e291–7.

[17] Kerner GS, van Dullemen LF, Wiegman EM, et al. Concurrent gemcitabine and 3D radiotherapy in patients with stage III unresectable non-small cell lung cancer. Radiat Oncol 2014;9. 190-717X-9-190.

[18] Turrisi 3rd AT, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 1999;340:265–71.

[19] Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 1999;341:476–84.

[20] Le Pechoux C, Dunant A, Senan S, et al. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99–01, EORTC 22003–08004, RTOG 0212, and IFCT 99–01): a randomised clinical trial. Lancet Oncol 2009;10:467–74.

[21] Ransom E, Joshi M, Nash D, Ransom B. The healthcare quality book: vision, strategy, and tools. Chicago: Health Administration Press; 2008.

[22] Roelofs E, Dekker A, Meldolesi E, van Stiphout RG, Valentini V, Lambin P. International data-sharing for radiotherapy research: an open-source based infrastructure for multicentric clinical data mining. Radiother Oncol 2014;110:370–4.

[23] Christodoulou M, McCloskey P, Stones N, et al. Investigation of a patient reported outcome tool to assess radiotherapy-related toxicity prospectively in patients with lung cancer. Radiother Oncol 2014;112:244–9.

[24] Xu C.J., van der Schaaf A., Schilstra C., Langendijk J.A., van't Veld A.A. Impact of statistical learning methods on the predictive power of multivariate normal tissue complication probability models. Int J Radiat Oncol Biol Phys 2012;82:e677–84.

[25] van der Schaaf A, Xu CJ, van Luijk P, van't Veld AA, Langendijk JA, Schilstra C. Multivariate modeling of complications with data driven variable selection: guarding against overfitting and effects of data set size. Radiother Oncol 2012;105:115–21.