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SHORT COMMUNICATION

Simultaneously modulated accelerated radiation therapy reduces severe oesophageal toxicity in concomitant chemoradiotherapy of locally advanced non-small-cell lung cancer

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Objective: The aim of this study was to evaluate the potential of simultaneously modulated accelerated radiation therapy (SMART) to reduce the incidence of severe acute oesophagitis in the treatment of unresectable locally advanced non-small-cell lung cancer (LANSCLC).

Methods: 21 patients were treated with SMART and concomitant platinum-based chemotherapy. The prescribed doses were limited to 54 Gy at 1.8 Gy per day to the zones of presumed microscopic extent while simultaneously maintaining doses of 66 Gy at 2.2 Gy per day to the macroscopic disease. The whole treatment was delivered over 30 fractions and 6 weeks. Dosimetric parameters of SMART and the standard technique of irradiation [intensity-modulated radiation therapy (IMRT)] were compared. Acute toxicity was prospectively recorded.

Results: The highest grade of oesophagitis was 62% (13 patients) grade 1, 33% (7 patients) grade 2 and 5%

(1 patient) grade 3. Three (14%) patients experienced acute grade 2 pneumonitis. There was no grade 4 oesophageal or pulmonary toxicity. Doses to the organs at risk were significantly reduced in SMART compared with IMRT [oesophagus: $V_{50\text{Gy}}$, 28.5 Gy vs 39.9 Gy ($p = 0.003$); $V_{60\text{Gy}}$, 7.1 Gy vs 30.7 Gy ($p = 0.003$); lung: $V_{20\text{Gy}}$, 27.4 Gy vs 30.1 Gy ($p = 0.002$); heart: $V_{40\text{Gy}}$, 7.3 Gy vs 10.7 Gy ($p = 0.006$); spine: D_{max} , 42.4 Gy vs 46.4 Gy ($p = 0.003$)]. With a median follow-up of 18 months (6–33 months), the 1-year local control rate was 70% and the disease-free survival rate was 47%.

Conclusion: SMART reduces the incidence of severe oesophagitis and improves the whole dosimetric predictors of toxicity for the lung, heart and spine.

Advances in knowledge: Our study shows that SMART optimizes the therapeutic ratio in the treatment of LANSCLC, opening a window for dose intensification.

INTRODUCTION

Concurrent chemoradiotherapy is the standard of care for the treatment of unresectable locally advanced non-small-cell lung cancer (LANSCLC).¹ Acute oesophageal toxicity (AET) is the main acute limiting toxicity related to this approach, and is responsible for weight loss, insertion of tube feeding, hospital admissions and treatment discontinuation.² A recent meta-analysis showed that hyperfractionated or accelerated radiotherapy (RT) schedules improve survival rates;³ however, when chemotherapy is associated concomitantly with these schedules, the incidence of severe oesophagitis of around 22% remains a subject of concern.⁴

In the RT planning process, the delineation of target volumes to be treated is an obligatory step. The gross demonstrable

disease is named gross tumour volume (GTV) and encompasses the primary tumour and the metastatic lymph nodes identified by the endoscopic and radiologic examinations. The microscopic tumour spread, outside of what can be visualized in a particular imaging modality, is named clinical target volume (CTV) and corresponds to a volume of tissue surrounding the primary tumour and the lymph node stations considered at risk of failure.⁵ In the standard technique of RT, a homogeneous dose of 66 Gy at 2 or 1.8 Gy per fraction and per day is delivered to the GTV and CTV. In contrast to this standard technique, simultaneously modulated accelerated radiation therapy (SMART) is a technique delivering 66 Gy by using high fraction doses (2.2 Gy per fraction) to the GTV simultaneously with standard fraction doses (1.8 Gy per fraction) to regions of

presumed microscopic extent (CTV), devised in such a manner that the biologically effective GTV dose is equivalent to 70 Gy delivered by conventional (2 Gy per fraction) fractionated RT. This regimen is delivered over 6 weeks, representing a moderate acceleration over a standard course. As proved in head and neck cancer, this technique lead to a moderate GTV dose acceleration without increasing acute or late toxicity and maintaining tumour control benefits associated with a shortened overall treatment time (acceleration).⁶

Nowadays, the standard recommendation is to deliver a homogeneous dose to the GTV and CTV.⁷ The aim of the present observational study was to evaluate the potential of SMART combined with concurrent chemotherapy, limiting the dose on the CTV to 54 Gy (1.8 Gy per fraction), in order to reduce the incidence of severe oesophagitis while maintaining local control (LC).

METHODS AND MATERIALS

Patients' characteristics and treatment

From August 2011 until July 2014, a total of 21 patients (patients) with histologically proven unresectable N2–N3 stage LANSCLC were treated with concomitant platinum-based chemotherapy and SMART. All patients had a physical examination, a chest, abdomen and pelvis CT scan, a fluorine-18 fludeoxyglucose positron emission tomography (¹⁸F-FDG-PET) scan, a bronchoscopy and pulmonary function tests at diagnosis. A lymph node biopsy guided by endoscopic ultrasound was indicated in order to confirm the N2–N3 status when considered necessary.

All patients were immobilized in the supine position. 10-respiratory-phase 4D-CT scan data sets were reconstructed with 2-mm slices. The GTV was delineated on each respiratory phase. An ¹⁸F-FDG-PET scan was used as an additional tool for GTV delineation. *GTV definition*: the primary tumour and clinically positive lymph nodes seen either on the planning CT (>1-cm short axis diameter) or pre-treatment ¹⁸F-FDG-PET scan (standardized uptake value >3) constituted the GTV. *Internal target volume definition*: the internal target volume definition (ITV) was obtained for the primary tumour from the 10 phases

of the 4D-CT scan. *CTV definition*: for the primary tumour, CTV was defined as the ITV plus a 5-mm margin to account for microscopic extension. The lymph node levels containing positive lymph nodes (selective nodal irradiation), and lymph node levels adjacent to invaded nodal stations were considered as CTV for a second dose level. Elective treatment of the mediastinum and supraclavicular fossae was not allowed. A 7-mm margin was used to create the planning target volume (PTV). Intensity-modulated plans were created using a step and shoot technique. The Pinnacle® v. 9.4 treatment-planning system (Philips Medical Systems, Best, Netherlands) equipped with the collapse cone convolution superposition dose calculation algorithm was used. *Dose prescription*: two dose levels were used. The PTV containing the primary tumour and clinically positive lymph nodes (PTV 66 Gy) received 66 Gy at 2.2 Gy per day. Lymph node levels containing metastatic lymph nodes (PTV 54 Gy) were treated to 54 Gy at 1.8 Gy per day (Figure 1). The prescribed doses were delivered simultaneously in 30 fractions, 5 days a week, over 6 weeks. For dosimetric comparison purposes, a trial called "standard technique" [intensity-modulated radiation therapy (IMRT)] was created prescribing a homogeneous dose of 66 Gy to a PTV containing the GTV + ITV + CTV + 7-mm margin. In both cases, the following constraints were applied to the organs at risk (OARs): total lung (total normal lung volume excluding the CTV), $V_{5Gy} < 65\%$, $V_{20Gy} < 30\%$; mean lung dose <20 Gy; spinal cord maximal dose ($D_2\%$) <45 Gy; oesophagus $V_{50Gy} \leq 30\%$ and heart $V_{Gy} < 50\%$. *Image-guided radiotherapy protocol*: an off-line image-guided radiotherapy (IGRT) protocol was used. Cone beam CT images were obtained daily on the first 3 days and then weekly. Region-of-interest for fusion was set to encompass the carina, adjacent vertebral bodies and the GTV. After registration, the translational corrections were applied to the treatment couch. If all the variances were <5 mm, the treatment proceeds without correction. If one or more corrections were >5 mm, adjustment was necessary prior to treatment, and a daily imaging with online corrections was allowed.

Data collection and statistics

Toxicities were assessed prospectively in terms of duration and severity. AET was recorded as the maximum acute oesophagitis

Figure 1. Planning CT–positron emission tomography fusion showing the gross tumour volume corresponding to a metastatic lymph node (1) and involved lymph node station (2); the corresponding planning target volume is shown in 3 and 4 lines, respectively. The oesophagus is shown using the 5 line. (a) Isodose line representing 95% of the 66-Gy prescription in a standard technique (intensity-modulated radiation therapy) at 2 Gy per fraction (6); (b) isodose line representing 95% of the 66-Gy prescription at 2.2 Gy per fraction (6); and the 54-Gy prescription at 1.8 Gy per fraction (7) in simultaneously modulated accelerated radiation therapy.

and acute lung toxicity as the first recorded treatment-related pneumonitis experienced. Toxicity was scored according to the Common Terminology Criteria for Adverse Events (CTCAE) 4.0. A dosimetric comparison between SMART and IMRT was performed in the first 12 patients. Disease-free survival (DFS) and LC rates were estimated using the Kaplan–Meier method, and the Wilcoxon test was used for matched pair analyses. The XLSTAT (Addinsoft 2013, Paris, France) software was used for statistical analysis.

RESULTS

The most prevalent toxicity observed was oesophagitis. The highest grade of oesophagitis scores during and after treatment was 62% (13 patients) grade 1, 33% (7 patients) grade 2 and 5% (1 patient) grade 3. The median duration of symptoms was 8 days (range 5–21 days), with the more severe grade recovering completely until day 21 after the end of RT. Three (14%) patients experienced acute grade 2 pneumonitis. There was no grade 4 oesophageal or grade 3–4 pulmonary toxicity, and no patient died of treatment-related causes. The median overall treatment time was 42 days (range 40–52 days). All patients received the intended dose of RT, and 15% required adjustments of the chemotherapy doses because of haematological or renal toxicity. There were no interruptions, except for 2 patients who presented events not related to the radiotherapy treatment (1 patient with spontaneous bacterial peritonitis and 1 patient with *Clostridium difficile*-associated diarrhoea). The length of these interruptions was 7 and 3 days, respectively. In the dosimetric analysis, doses to the different OARs were significantly reduced with SMART when compared with IMRT (Table 1).

With a median follow-up of 18 months (6–33 months), the estimated 1 year LC rate was 70% (95% CI, 48–89%) and the DFS rate was 47% (95% CI, 22–71%). Five patients presented an isolated local recurrence (LR), three presented a metastatic disease associated with a local or regional recurrence, and two presented a systemic failure without LR. There were no isolated lymph node recurrences. All local recurrences occurred within the volume of the 95% isodose prescription line. There were no marginal recurrences.

DISCUSSION

In this study, we showed a significant reduction in the incidence of AET using an accelerated RT schedule with concomitant chemotherapy. These results are mainly related to the dose levels tailored according to the tumour burden. With SMART, the dose delivered to the microscopic disease is limited to 54 Gy, which is largely recognized

as a sufficiently effective dose to sterilize microscopic disease, while keeping high doses (66 Gy) to areas of macroscopic disease (Figure 1). In fact, doses around 54 Gy are considered the standard of care in the adjuvant treatment of lung cancer and other anatomic localizations.⁸ There is a general agreement about target volumes that should be treated in LANSCLC, and homogeneous doses to the macroscopic and microscopic disease of 66 Gy are the standard recommendations.⁷ However, doses delivered are usually limited to 60 Gy because of constraints to the OARs. With SMART, the possibility to adapt dose levels according to the tumour burden allows significant dose reduction to the oesophagus and also to the lung, heart and spine (Table 1). In our study, we delivered the intended doses to the targets while respecting OAR constraints in most cases. Moreover, in a considerable number of cases, the limited doses delivered to the different OARs could open a window for dose intensification.

With only 5% of grade 3 oesophagitis, our results compare favorably with those reported in the literature,^{3,4} indicating that the dosimetric gain has a clinical impact on the incidence of AET. Even if acute oesophagitis has been considered reversible, it is responsible for treatment interruptions and dose reductions. In fact a recent publication⁹ showed a consequential effect between acute oesophagitis intensity and late oesophageal strictures. Therefore, a reduction in the incidence of severe oesophageal toxicity remains a major clinical concern in thoracic irradiation.

In our analysis of lung toxicity, there was no severe (grade 3–4) pneumonitis, and the 14% rate of grade 2 pneumonitis compares quite favourably with those reported with IMRT.¹⁰ Our results are in line with the significant improvement of the dosimetric parameters with SMART.

The LC and DFS rates of our cohort are comparable to those published in the literature³ suggesting a potential benefit in the therapeutic ratio. We emphasize the absence of isolated mediastinal recurrences that we explain mainly by two factors: first, the mediastinal extension was carefully documented by ¹⁸F-FDG-PET scan and endoscopic ultrasound, and second, because doses were effectively delivered through a very conformal and high-precision technique (SMART and IGRT combination). Isolated mediastinal lymph node recurrences are infrequent. Similar to our findings, Schytte et al¹¹ found only 1 isolated mediastinal recurrence over 93 patients analysed for locoregional failure, with most recurrences being in the intrapulmonary tumour volume.

Table 1. Dosimetric parameters in case of simultaneously modulated accelerated radiation therapy (SMART) and intensity-modulated radiation therapy (IMRT)

RT technique	Oesophagus		Lung			Heart	Spine
	V _{50Gy}	V _{60Gy}	V _{5Gy}	V _{20Gy}	Mean dose	V _{40Gy}	D _{max} , Gy
	Mean (range)						
SMART	28.5 (15.6–42)	7.1 (0–34)	60.6 (45–77)	27.4 (20–34)	14.3 (9.7–17.4)	7.3 (0–28)	42.4 (36.8–47.6)
IMRT	39.9 (28–58.3)	30.7 (18–47)	61.9 (47.6–78)	30.1 (22–36)	15.7 (11–18.7)	10.7 (0–28.4)	46.1 (39–50.7)
p-value	0.003	0.003	0.03	0.002	0.002	0.006	0.003

D_{max}, maximal absorbed dose in 2% of the structure; RT, radiotherapy; SMART, simultaneously modulated accelerated radiation therapy; V_{50Gy}, V_{60Gy}, V_{5Gy}, V_{20Gy} and V_{40Gy} volumes of the normal structure that received 50, 60, 5, 20 and 40 Gy, respectively.

The utility of elective nodal irradiation remains controversial because of a low rate (around 6%) of isolated nodal failures beyond the RT field.¹² Therefore, an irradiation limited to the involved lymph node stations is usually recommended.¹³ However, the clinical experience validating this approach were obtained with older techniques delivering a considerable “incidental dose” to the uninvolved mediastinal lymph nodes.¹⁴ With more recent techniques such as SMART, the fast fall-off of dose improves our ability to restrict dose to the target. The reduction of such an “incidental dose” may have unintended negative consequences regarding regional control, therefore, a careful definition of the volumes to be treated is crucial and dose reductions should be performed carefully. In our study, we consider it reasonable to limit the dose to 54 Gy to areas of microscopic tumour burden, instead of the standard recommendations, in which the whole macroscopic and microscopic disease is treated to a homogeneous dose of 66 Gy.

We recognize, the small number of patients in our study is the main constraint; however, the significant improvement of the dosimetric results and their clear clinical impact justify the

continuation of this prospective study integrating dose intensification in the next step.

Finally, Lievens et al¹⁵ has shown in a dosimetric study and using a standard technique of irradiation with one dose level that the oesophagus is the main constraint limiting dose escalation. More disturbing are the disappointing results of the RTOG 0617 trial. This trial compared the standard dose of 60–74 Gy in a standard fractionation.¹⁶ Overall survival was inferior in the high dose arm, probably because of a higher rate of toxicity. In this context, tumour-burden dose intensification strategies, such as those proposed in SMART, warrant further investigation in the research of therapeutic ratio optimization for the treatment of LANSCLC.

CONCLUSION

This sophisticated radiotherapy technique reduces the incidence of severe oesophagitis and improves the overall dosimetric predictors of toxicity for the lung, heart and spine. SMART optimizes the therapeutic ratio, opening a window for dose intensification in the treatment of LANSCLC.

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