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FULL PAPER

Dose escalation in extracranial stereotactic ablative radiotherapy (DESTROY-1): A multiarm Phase I trial

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Objective: A multiarm Phase I clinical trial was performed to define the maximum tolerated dose (MTD) of stereotactic body radiotherapy (SBRT) delivered by non-coplanar conformal beams or volumetric modulated arc therapy technique in seven predefined clinical settings.

Methods: The (a) and (b) arms investigated primary and metastatic lung cancer differentiated by site of onset, arm (c) included primary or metastatic lesions outside the thorax, the (d) and (e) arms were for in-field reirradiation of recurrence, and finally, the (f) and (g) arms were for boost irradiation to the lesions after an adjuvant RT prescribed dose. A 4 months cut-off after previous irradiation course was fixed to distinguish the boost from the retreatment (≤ 4 vs > 4 months, respectively). Patients were prospectively enrolled in study arms according to tumor site, clinical stage and previous treatment. The total dose prescribed to the isocenter, ranged from 20 to 50 Gy according to the protocol design and the doses per fraction ranged from 4 to 10 Gy in 5 days.

Results: A total of 281 patients (M/F: 167/114; median age: 69 years) with 376 lesions underwent SBRT. No acute toxicity was reported in 175 patients (62.3%) while 106 (37.7%) experienced only low-grade ($G < 2$) acute toxicity. Four patients (all previously irradiated in the same site) showed $> \text{Grade } 2$ toxicity within 6 months from SBRT. With a median follow-up of 19 months, 204 patients (72.6%) did not experience late toxicity, and 77 (27.4%) experienced low grade late toxicity. On per-lesion basis, the 12- and 24 months actuarial local control inside the SBRT field were 84.3 and 73.7 %, respectively.

Conclusions: SBRT delivered in five consecutive fractions up to the doses evaluated is well tolerated. The MTD was reached in four (a, b, c and f) of the seven study arms. Recruitment for (d), (e) and (g) arms is still ongoing.

Advances in knowledge: In a prospective dose-escalation trial, the MTD of 50 Gy/10 Gy fraction and 35 Gy/7 Gy fraction were defined for primary and metastatic lesions and as boost after prior RT dose ≤ 50 Gy, respectively.

INTRODUCTION

Stereotactic body radiation therapy (SBRT) is an advanced technique that allows the irradiation of small, precisely defined targets with high radiotherapy (RT) doses in a single or a few sessions while sparing the surrounding normal tissue.¹⁻⁴

The role of SBRT has been recognized of significant importance in two clinical settings: (i) early stage of primary cancer judged unfit for surgery or other aggressive local

treatment (ii) oligometastatic disease, a state of limited systemic metastatic tumors for which local ablative therapy could be curative⁵ although with significant commonalities and controversies for patient selection and follow-up recommendations.

In particular, SBRT has been reported in the treatment of early-stage lung,⁶ liver,⁷ prostate,⁸ renal-cell and pancreatic^{9,10} cancers, as well as lung,¹¹ liver,⁷ abdominal nodes,¹² spine,¹³ breast and gynaecological^{14,15} oligometastases.

During the past decade, there has been an upsurge in the use of SBRT with a relative lack of clinical evidence documenting efficacy, appropriate indications, and clinical guidelines for best practices.^{16,17} Several dose and fractionation schedules have been proposed, mostly on the basis of clinical experience acquired in few referral centers.^{16,17} Indeed, the tolerability of SBRT is strictly related to the anatomic site, surroundings organs at risk and previous irradiation at the same site. However, the evidences on the optimal dose and fractionation in various clinical settings are relatively scarce, as well as Phase I studies aimed at defining the maximum tolerated dose (MTD). Formal dose-escalation studies defining effective treatment boundaries in a shorter period while exposing fewer patients to either too low or too high dose levels are of significant importance to extend the indications of SBRT by showing the true potential of this technique.

Thus, in the early 2000s, we conceived and set into practice a prospective Phase I study aimed to define the MTD of SBRT in seven predefined clinical settings different from each other for involved OARs and previous in-field irradiation.

The purpose of this report is to present the results in terms of safety and efficacy of overall personal SBRT experience, however, because of the unexpected excessively long accrual, the final results of the four closed arms are reported and discussed, while the interim results of the arms still ongoing are described at the reached dose level.

METHODS AND MATERIALS

Dose Escalation STereotactic RadiOtherapy-1 (DESTROY-1) was a prospective Phase I study in primary or oligometastatic (≤ 5 lesions) cancer patients. The trial was approved by the Catholic University Institutional Review Board (Destroy-1: P#594/CE) and all patients signed a written informed consent.

The clinical trial design included seven arms enrolling different patients according to tumor site, clinical stage and previous treatment as reported in Table 1. The (a) and (b) arms were conceived for primary and metastatic lung cancer differentiated by site of onset: intraparenchymal lesions (a) where dose was escalated up

to 50 Gy in four levels and paramediastinal or near chest wall lesions (b), defined as target within 1 cm in all directions of any mediastinal critical structure or chest wall, where the dose was escalated up to 50 Gy in six levels. The arm (c) was conceived for primary or metastatic lesions arising outside the thorax, therefore, collected a miscellanea of nodal lesions from head and neck, thoracic, abdominal and pelvic cancers, liver and adrenal metastases, primary prostate and pancreatic cancer unfit for surgery or other aggressive local treatment. The (d) and (e) arms were conceived for retreatment of recurrence after prior RT and were differentiated as follows: in arm (d), recurrences pre-irradiated with dose >60 Gy or recurrences in sites with previous small bowel irradiation were included, while in arm (e) recurrences in sites receiving a prior RT dose ≤ 60 Gy were enrolled. Maximal dose was set to 45 Gy in arm (d) and 50 Gy in arm (e) in six levels, respectively. Finally, the (f) and (g) arms were to boost lesions with a prior RT dose ≤ 50 Gy (f) or >50 Gy (g), and dose was escalated up to 35 Gy (f) or 30 Gy (g) in 3 levels, respectively. A 4 months cut-off after previous irradiation was fixed to distinguish the boost from the retreatment (≤ 4 vs >4 months, respectively). Supportive therapy was prescribed according to the irradiated site as previously described.¹⁸ Late toxicities were continuously monitored even in patients showing progressive disease.¹⁹

Study objectives

The MTD of SBRT performed by non-coplanar conformal beams or volumetric modulated arc therapy (VMAT) technique in predefined clinical settings was the primary end point of the study, whereas safety, efficacy and evaluation of local control were the secondary objectives.

Study design

A dose escalation design was used to identify the MTD. Each cohort was evaluated for dose-limiting toxicity (DLT) and consisted of 6 patients, if one of the patients experienced a DLT, the cohort was expanded to 12 patients. DLT was defined as any radiation-related $\geq$ Grade 3 toxicity (RTOG criteria¹⁹) occurring within 6 months from SBRT. Adverse events occurring later than 6 months after SBRT were described as late toxicities,

Table 1. Study arms with planned and reached dose levels (bold)

Dose levels (Gy)				Retreatment		Boost	
	(a)	(b)	(c) ^a	(d) ^b	(e)	(f)	(g)
I	25/5	25/5	25/5	20/4	25/5	25/5	20/4
II	37.5/7.5	30/6	30/6	25/5	30/6	30/6	25/5
III	45/7	35/7	35/7	30/6	35/7	35/7	30/6
IV	50/10	40/8	40/8	35/7	40/8		
V		45/9	45/9	40/8	45/9		
VI		50/10	50/10	45/9	50/10		

(a) primary and metastatic lung intraparenchymal tumours; (b) paramediastinal or near chest wall primary and metastatic lung parenchymal tumours; (c) primary or metastatic cancers arising outside the thorax; (d) previous RT >60 Gy; (e) previous RT ≤ 60 Gy; (f) after RT ≤ 50 Gy; (g) after RT >50 Gy. Total and *per* fraction dose are reported in Gy.

^aLymph nodal disease (H&N, thorax, abdomen, pelvic), liver and adrenal metastases, prostate and pancreatic cancer.

^bOr previous small bowel irradiation.

but not considered in DLT evaluation. The MTD was defined as the highest dose level at which DLT was observed in ≥ 2 of 6 patients or the final dose cohort reached. An upper limit was preselected at the time of study design as the highest dose level to be evaluated.

The total dose, prescribed to the target isocenter (International Commission on Radiation Units and Measurements-ICRU report 62 and report 83), ranged from 20 to 50 Gy (biologic effective dose, $BED_{2Gy} = 28\text{--}100$ Gy, $\alpha/\beta = 10$) according to the different arms of the protocol; the doses per fraction ranged from 4 to 10 Gy in 5 days.

Eligibility

Patients were accrued according to the following inclusion criteria: (i) histological diagnosis of solid tumor, (ii) age >18 years, (iii) adequate performance status (ECOG 0–3), (iv) adequate bone marrow, liver and renal function. Adequate bone marrow was defined as follows: neutrophil count $>1500/\text{ml}$, platelets $>100,000/\text{ml}$, hemoglobin $>9\text{ g dl}^{-1}$. Moreover, for patients irradiated in the lumbar/abdominal area: creatinine $<1.8\text{ mg dl}^{-1}$; for patients irradiated in the liver: total bilirubin $<3\text{ mg dl}^{-1}$, lactate dehydrogenase $<3 \times$ normal value, aspartate transaminase $<3 \times$ normal value, alanine transaminase $<3 \times$ normal value, alkaline phosphatase $<3 \times$ normal value. Previous surgery and/or chemotherapy and/or RT were accepted. Patients with ECOG >3 or medical problems unrelated to malignancy which would limit full compliance with the study, and previous SBRT were excluded.

Simulation and region of interest (ROI) contouring

CT simulation scans were acquired at 3-mm interval in the target region. Patients were treated with the Elekta Stereotactic Body Frame (SBF; Elekta Oncology Systems, Crawley, UK) based on a stereotactic system of coordinates for target position instead of anatomical landmarks. The clinical target volume was defined as the gross tumor volume identified on CT and/or CT-PET and/or MRI. A 5 mm margin was added to the gross tumor volume in lung and liver primary tumors. Diagnostic and simulation images were reviewed by a dedicated radiologist (GS). The internal target volume definition was based on respiratory excursions analysis (free breathing or abdominal compression/active breathing coordinator), while the set-up margin was set at 3 mm for all patients after three CT scan evaluations of set-up reproducibility, as previously described.¹⁸ Intravenous and *per os* contrast medium were used in selected cases.

Treatment planning

Treatment plans were optimized using the Precise-Plan treatment planning system (TPS) v. 2.16 and the ERGO ++ TPS for VMAT technique (Elekta, Crawley, England), as previously described.^{14,15,18,20,21}

In particular, the first 152 lesions were treated according to a class solution based on a tetrahedral static beam configuration.^{15,20} Subsequently, 224 lesions were treated with the VMAT technique.^{14,18} According to the study design, the only dose-volume

constraints were for spinal cord ($D_{\text{max}} <30$ Gy; EQD_{2Gy} , $\alpha/\beta:3 = 54$ Gy) and small bowel ($V30Gy <1$ cc; EQD_{2Gy} , $\alpha/\beta:3 = 54$ Gy).

For quality assurance of treatment planning and delivery, two Independent Checks (IC1 and IC2) were carried out by medical and physical staffs,²² moreover, all plans underwent pretreatment dose verification.²¹

Response assessment

4 months after SBRT treatment, the response was evaluated by morphological (contrast-enhanced CT scan and/or MRI) or functional imaging modalities (18F-fluodeoxyglucose-PET or choline PET for prostate cancer).

Objective tumor response was assessed at 4 months, a timing suitable for both early and late responder malignancies, according to the RECIST (Response Evaluation Criteria in Solid Tumors) system v1.0²³ and/or EORTC (European Organization for Research and Treatment of Cancer) criteria²⁴ as previously detailed.²⁵

Statistical analysis

The sum of complete and partial response was considered the objective response rate (ORR), while the sum of ORR and stable disease was defined as clinical benefit. The 95% confidence intervals (95% CI) have been provided.

Local control of irradiated lesions was calculated using the Kaplan-Meier method²⁶ from the date of SBRT to the date of the in-field relapse/progression of disease or the last seen date. Metastasis-free survival was calculated on per patient basis from the date of SBRT to the date of relapse/progression outside SBRT field or the last seen date. Statistical analysis was carried out using SYSTAT, v. 11.0 (SPSS, Chicago, IL).

RESULTS

281 patients with 376 lesions underwent SBRT on consecutive weekdays between July 2003 and February 2017. Clinicopathological characteristics of the whole population and treatment details are summarized in Table 2. The male/female ratio was 167/114 and the median age was 69 years (range: 35–90 years). The most frequent primary tumor was lung (27.9%), followed by gynecological (25.3%), gastrointestinal (21%), and genitourinary cancer (13.3%). 209 patients (74.4%) received SBRT on a single lesion, whereas 54 (19.2%), 15 (5.3%), 2 (0.7%) and 1 (0.4%) patients were irradiated on two, three, four or six different metastatic sites, respectively, thus leading to a total number of 376 treated lesions. The median planning target volume ranged from 1.45 to 281.2 cc (median: 32.36 cc). The SBRT prescribed dose ranged from 20 to 50 Gy ($BED_{2Gy} = 28\text{--}100$ Gy, $\alpha/\beta = 10$).

Main findings

The MTD was defined in 4 (a, b, c and f) of the 7 arms, while patients enrollment in (d), (e) and (g) arms is still ongoing (Table 3). In arm (a), where 32 intraparenchymal targets were irradiated at 4 different dose levels (Table 3), 50 Gy in 10 Gy per fraction were delivered without any DLT. In arm (b), where 83 paramediastinal or near the chest wall primary and metastatic

Table 2. Patients' characteristics and treatment details

	No. patients (%)	No. lesions (%)
	281	376
Male/female ratio	167/114 (59.4/40.6)	
Age, years, median (range)	69 (35–90)	
Neoplasm		
Lung cancer	89 (31.7)	105 (27.9)
Gynecologic cancer	58 (20.6)	95 (25.3)
Gastrointestinal cancer	61 (21.7)	79 (21)
Genitourinary cancer	40 (14.2)	50 (13.3)
Breast cancer	15 (5.3)	23 (6.1)
Head & neck cancer	12 (4.3)	15 (4)
Miscellanea	6 (2.2)	9 (2.4)
Type of lesion (%)		
Lymph node metastasis	132 (47)	188 (50)
Primary or metastatic lung tumors	97 (34.5)	119 (31.6)
Liver metastases	4 (1.4)	13 (3.5)
Other	48 (17.1)	56 (14.9)
Planning target volume (cc), median (range)		32.36 (1.45–281.2)
SBRT dose (Gy), range (BED _{2Gy} ^a α/β:10)		20–50 (28–100)

BED, biologically effective dose; SBRT, stereotactic body radiotherapy;

lung parenchymal tumours were irradiated at six different dose levels, 50 Gy in 10 Gy per fraction were delivered without any DLT. In arm (c), where 106 lesions from primary or metastatic

cancers arising outside the thorax were irradiated at six different dose levels, 50 Gy in 10 Gy per fraction were delivered without any DLT. This arm included 73 nodal sites (H&N, thorax, abdomen, pelvic), 18 liver and adrenal metastases, 5 pancreatic cancer, 4 prostate cancers and other 6 various lesions.

In arm (f), in which a SBRT boost after prior RT dose ≤ 50 Gy was delivered at three different dose levels, up to 35 Gy in 7 Gy per fraction were delivered to 41 lesions with only 1 DLT (see below).

Concerning the still ongoing arms (d, e and g), the reached dose levels are detailed in Table 3 and their DLTs described in the safety analysis.

Safety

All patients received the prescribed SBRT treatment and were included in the safety analysis. Details concerning the time of onset, type and severity of complications are provided in Table 4.

175 patients (62.3%) did not experience any acute toxicity, while 106 (37.7%) mainly experienced low grade acute toxicity with no patient showing >G2 toxicity. Four patients showed >Grade 2 toxicity within 6 months from SBRT. Notably, the four patients showing DLT had been previously irradiated at the same site. In details, one patient (arm d) with recurrent sacral chordoma, previously treated by pelvic intensity-modulated RT dose of 98.9 Gy (EQD_{2Gy} α/β:3), received a 30 Gy SBRT retreatment. 4 months after irradiation, she developed an abscess in the sacral region that was treated by drainage and local medications and healed by secondary intention.

One patient (arm f) with a pancreatic cancer unfit for surgery, received a 35 Gy SBRT boost on pancreatic head after a previous RT treatment of 30 Gy/3 Gy fraction at the same site. 6 months

Table 3. Dose limiting toxicity and maximum tolerated dose according to different arms

Total dose/fraction (Gy)	No. of dose limiting toxicity per no. of lesions							
	Retreatment					Boost		
	(a)	(b)	(c) #	(d) ##	(e)	(f)	(g)	All
20/4				0/6			0/9	0/15
25/5	0/6	0/6	0/6	0/6	0/6	0/10	1/12	1/52
30/6		0/7	0/28	1/16	0/7	0/13	n.r.	1/71
35/7		0/11	0/26	0/15	0/10	1/18	n.r.	1/80
37.5/7.5	0/7							0/7
40/8		0/12	0/17	1/16	0/9			1/54
45/9	0/6	0/6	0/18	0/2	n.r.			0/32
50/10	0/13	0/41	0/11		n.r.			0/65
Total	0/32	0/83	0/106	2/61	0/32	1/41	1/21	4/376

n.r., not reached; (a) primary and metastatic lung intraparenchymal tumours; (b) paramediastinal or near chest wall primary and metastatic lung parenchymal tumours; (c) primary or metastatic cancers arising outside the thorax; (d) previous RT >60 Gy; (e) previous RT ≤60 Gy; (f) after RT ≤50 Gy; (g) after RT >50 Gy;

^aLymph nodal disease (H&N, thorax, abdomen, pelvic), liver and adrenal metastases, prostate and pancreatic cancer;

^bOr previous small bowel irradiation.

Table 4. Type of acute and late toxicities according to organ system and grade

Organ system acute toxicity (RTOG scale)	No	Type
All events	133	
Skin	33	
Grade 1	24	Dermatitis radiation (N = 24)
Grade 2	9	Dermatitis radiation (N = 9)
Mucous membrane	3	
Grade 1	2	Oral mucositis (N = 2)
Grade 2	1	Oral mucositis (N = 1)
Pharynx & Esophagus	24	
Grade 1	17	Dysphagia (N = 3); Esophagitis (N = 14)
Grade 2	7	Dysphagia (N = 2); Esophagitis (N = 5)
Larynx	1	
Grade 1	1	Hoarseness (N = 1)
Lung	10	
Grade 1	10	Dyspnoea (N = 10)
Upper gastrointestinal tract	42	
Grade 1	42	Nausea (N = 42)
Lower gastrointestinal tract	16	
Grade 1	13	Diarrhea (N = 11); proctitis (N = 2)
Grade 2	3	Diarrhea (N = 1); proctitis (N = 2)
Genitourinary tract	4	
Grade 1	3	Frequency (N = 3)
Grade 2	1	Frequency (N = 1)
Organ system late toxicity (RTOG/EORTC scale)	No	Type
All	92	
Skin	12	
Grade 1	6	Skin hyperpigmentation (N = 6)
Grade 2	6	Skin hyperpigmentation (N = 3); telangiectasia (N = 3)
Mucous membrane	1	
Grade 1	1	Vaginal atrophy (N = 1)
Subcutaneous tissues	5	
Grade 1	1	Slight in duration (N = 1)
Grade 2	3	Moderate fibrosis (N = 3)
Grade 4	1	Presacral abscess (N = 1)
Lung	65	
Grade 1	51	Slight radiographic appearances of pneumonia (N = 51)

(Continued)

Table 4. (Continued)

Organ system acute toxicity (RTOG scale)	No	Type
Grade 2	14	Patchy radiographic appearances of pneumonia (N = 13); moderate symptomatic pneumonia (N = 1)
Small/large intestine	8	
Grade 1	3	Slight rectal bleeding (N = 3)
Grade 2	2	Intermittent rectal bleeding (N = 2)
Grade 3	2	Duodenal bleeding requiring surgery (N = 1); Colonic stenosis requiring surgery (N = 1)
Grade 5	1	Fistula (N = 1)
Genitourinary tract	1	
Grade 2	1	Macroscopic hematuria (N = 1)

All patients showing severe late toxicity ($\geq$ G3) had been previously irradiated at the same site

after SBRT, the patient required a biliary stent removal and during endoscopic retrograde cholangiopancreatography (CPRE), he showed a duodenal bleeding. As a consequence, a chemoembolization procedure was required and although bleeding during removal of a stent is reported among the CPRE complications, prudentially we considered this event as a Grade 3 late toxicity.

One endometrial cancer patient (arm g), previously irradiated on pelvic lymph nodes (45 Gy/1.8 Gy fraction) and on vaginal vault by concomitant boost (55 Gy/2.2 Gy fraction), underwent SBRT boost (25 Gy) on vaginal recurrence. She presented a colonic stenosis 4 months after SBRT and required ileostomy.

Finally, one rectal cancer patient (arm d) with a presacral recurrence underwent SBRT retreatment (40 Gy) after 3D-CRT dose of 84.4 Gy (EQD₂ Gy α/β :3) at the same site. 5 months later, he developed progressive disease with a presacral abscess unfit for surgery and subsequently he died because of a stercoral peritonitis. Also, in this case we are not sure if the abscess and the consequent peritonitis had been caused by the disease progression or by the high delivered doses, but again we preferred to consider it as a Grade 5 toxicity.

With a median follow-up of 19 months (range: 6–157 months), 204 patients (72.6%) did not experience any late toxicity, while 77 patients (27.4%) experienced mainly low-grade late toxicity. The 2 year grade $\geq$ 3 late-toxicity free survival was 98.9%.

36 (12.8%) patients with 44 lesions (11.7%) were deescalated (*i.e.* enrolled in one of the previous dose levels) for unacceptable bowel doses and none for spinal cord dose.

Table 5. Morphological and functional 4 months response assessment on a per lesion basis

	Morphological response (337 lesions)			Functional response (252 lesions)		
		No	%		No	%
Lesions	Overall response	159	47.1	Overall response	223	88.5
	Complete response	81	24.0	Complete response	146	57.9
	Partial response	78	23.1	Partial response	77	30.6
	Stable disease	168	49.9	Stable disease	20	7.9
	Progressive disease	10	3.0	Progressive disease	9	3.6

Efficacy

Overall efficacy analysis was performed with an inherent limit to a no specific site evaluation. The 4 months clinical response was evaluated in 337 of 376 lesions (89.6%) by morphological imaging (CT scan and/or MRI examinations). The ORR of target lesions was 47.1% [95% CI (41–53)] including 81 (24%) lesions achieving complete response and 78 (23.1%) lesions achieving partial response. Moreover, stable disease was observed in 168 [49.9%; 95% CI (44–55)] lesions, while SBRT in-field progression was documented in 10 [3%; 95% CI: (1.6–5.3)] lesions (Table 5).

The 4 months clinical response was evaluated in 252 of 376 lesions (67.0%) by functional imaging (PET-CT) along with morphological CT. The ORR of target lesions was 88.5% [95% CI (84–92)] including: 146 complete response (57.9%), 77 partial response (30.6%), 20 stable disease (7.9%), and 9 SBRT in-field progression (3.6%) (Table 5).

On per-lesion basis, the 12- and 24 months actuarial local control inside SBRT field were 84.3 and 73.7%, respectively (Figure 1).

Figure 1. The 1- and 2-year inside SBRT field disease control, expressed on a per lesion basis. SBRT, stereotactic body radiotherapy.

Out of field SBRT recurrence/progression was documented in 196 (52.1%) lesions. On per-lesions basis, the 2 year out of field SBRT progression-free survival was 42.1%.

DISCUSSION

The present dose-escalation study included 281 patients distributed in seven predefined clinical settings, exploring different anatomical districts and/or retreatment of previous irradiated sites. It represents a complex and articulated project that can be considered pioneering taking into account the period in which it was conceived (early 2000s). At the time of this analysis, the MTD was defined in four (a, b, c, f) of the seven study arms, while the patients' enrolment is still ongoing for arms (d), (e) and (g), whose results cannot therefore be considered conclusive. Each arm will be the subject of a next single detailed analysis, but in the present paper we present an overview of overall series, limiting the numerous possible considerations per arm to those that seem to us more meaningful and that may be of interest to the readers.

The relatively low dose choices (total and *per fraction*) in some arms could be considered a limit of this study if compared with more recent literature. In particular, this aspect is evident in the arm (a) because the most recent SBRT trials and guidelines on intraparenchymal lung cancer suggest higher doses/fractions that are more effective than those presented in our study.^{27–29} Indeed, we have to consider that the study was planned in 2003, when the evidences on the tolerability of SBRT were more limited and no safety studies neither guidelines or robust trials were available. Moreover, the lack of modern technology then such as cone beam, micromultileaf collimators and 4D-CT scan, prompted us to be more cautious. Therefore, at that time, we deemed it safer to set 50 Gy in five fractions as the limit for our arm (a) dose escalation.

In the arm (b) we assumed to achieve a dose of 50 Gy in 10 Gy per fraction, passing through several steps. In other words, at the time of the study design, we planned a different dose-escalation scheme according to mediastinal/chest wall or central lung lesions site. Thereafter, literature confirmed the need to use in the so-called “no-fly” zone a lower fractionation or several fractions compared to the peripheral ones.^{29–32} To date, the recommended dose in (b) arm is aligned with the literature and guidelines,³³ and we treated 83 lesions (41 of them with BED₁₀ ≥100 Gy) without any severe toxicity. One could argue that especially

for centrally located lung tumors, late toxicity as defined could have well contributed to DLT, therefore, particular attention is devoted into follow-up of these patients, and as of today they have not developed any other acute and late Grade 3 toxicities other than those described in the text.

The third completed arm (c) includes a miscellanea of cancer presentations, with a majority of nodal recurrences. The reached level (50 Gy/10 Gy fraction) is comparable with some recent series including abdomino-pelvic lymph-node metastases reporting doses ranging from 36 Gy/12 Gy *per fraction*³⁴ to 45 Gy/7.5 Gy *per fraction*.³⁵ Moreover, our experience is quite similar to Zeng and coll.³⁶ with a median of five 9-Gy fractions (median BED₁₀: 85.5 Gy) in patients with recurrent pancreatic carcinoma in abdominal nodes or stump after surgery. Although we are aware that this arm is biased by mixing different clinical settings, we judge our finding feasible and reproducible.

A further comment should be reserved to arm (f), whereas SBRT was used as boost after a RT dose ≤ 50 Gy, few experiences, mostly in lung or pancreatic cancer, have been reported in literature. Higgins and coll. in a Phase I study proposed a safe alternative of 10 Gy $\times$ 2 SBRT boost to both the primary tumor and involved mediastinal lymph nodes after 44 Gy of conventionally fractionated thoracic RT with concurrent chemotherapy.³⁷ A personal case series,²⁰ one prospective³⁸ and two retrospective studies^{39,40} previously tested a planned SBRT boost shortly after conventional chemoradiation in pancreatic cancer. Doses ranged from a single fraction of 14–25 Gy^{38,39} to a modest hypofractionation of 20–30 Gy in 3–5 fractions⁴⁰ and achieved comparable results in regards to acute and late grade ≥ 3 toxicities ranging from 0–13% to 0–7%, respectively. The current series, surely original because of the heterogeneous setting (lesions from gynecologic, lung and head & neck cancer), suggests that intensification with SBRT at the reached dose level (35 Gy at 7 Gy per fraction) appears to be a safe and reasonable option to increase local control in some relatively radioresistant neoplasms. Therefore, this potential new role of SBRT has been confirmed, although it requires great caution and expertise.

Concerning the arms still ongoing, to date, in the retreatment arms (d and e) and for a boost after >50 Gy arm (g), 40 Gy in five fractions and 25 Gy in five fractions were safely delivered, respectively. Unfortunately, the accrual was particularly slow in these arms, but they are particularly interested in testing the challenging topic of SBRT role in retreatment and dose-escalation. The OARs tolerance to extreme hypofractionation after conventional irradiation remains largely unknown and it must be emphasized that all DLTs in our study (4 out of 281 patients: 1.4%) were registered in previously irradiated patients. This finding should lead to a cautious attitude in this situation; in fact, reirradiation is a specific situation where variables in terms of time between treatments, volumes, previous general conditions add to the uncertainties related to the (really biological) cumulative doses of the two treatments. New ways of predicting toxicity based on the dose administered in the first and second irradiations, probably considering also the technique used in both, are warranted. Moreover, in patients for whom SBRT boost is

planned, the previous standard irradiation should be performed so as to minimize the subsequent risk of late toxicity, *e.g.* using highly conformed techniques and hyperfractionated regimens.

Doubts could be raised about the choice of 60 Gy cut-off to distinguish arm (d) from arm (e); indeed, it represents an arbitrary cut-off chosen at the time of study design to distinguish neoadjuvant-adjuvant treatments from radical ones. In our opinion, a single arm including all retreatments ($>$ or <60 Gy) would have provided little useful information to readers, due to the large variability of the previous delivered doses (patients could have been treated with doses ranging from 25 to 70 Gy). Therefore, to assess SBRT feasibility and limitations in retreatment setting we chose to distinguish patients who received a low-to-medium dose from those who received a high dose, fixing 60 Gy as arbitrary divergent dose.

A further arbitrary choice was done in fixing a 4 months cut-off to distinguish between retreatment and boost, mostly due to the absence of general rules to distinguish those overdoses in temporal terms. We considered unlikely that an irradiated tumor requires a retreatment before 4 months from previous RT, on the other hand, we chose to take into account the setting of patients who underwent adjuvant systemic therapies at the end of standard RT, in which a “delay” of the boost could be justified. For example, in the case of slow-response tumors such as pancreatic carcinomas, a “delayed” boost could allow a tailored overdosage to the residual neoplasm after a suitable time interval.

In terms of efficacy, the reported data on 2-year SBRT in-field disease control (73.7%) are unsatisfying if we considered the site-specific performance of the technique according to literature. Caution is needed in comparing a cumulative local control with a single well studied clinical setting, otherwise results could be misleading. The reported local control rate has to be considered only as an overview of the SBRT efficacy, *i.e.* a way to generally present and discuss advantages of extracranial SBRT in predefined settings. For peripheral lung tumors, *e.g.* it is commonly accepted that a BED₁₀ ≥ 100 Gy on the surrounding isodose is well tolerated and necessary to achieve $>90\%$ local control after 2 years^{27–29,41}; in our trial, only the highest dose level had satisfied this constraint reaching a 2-year SBRT in-field disease control of 88.9% (data not shown). For abdominal sites, on the contrary, the 2-year SBRT in-field disease control observed in this experience was encouraging and comparable with the ones (70–90%) reported by other studies.^{7,11,42,43} Additional cancer-based evaluation of the dose–response relationship seems warranted in order to optimize dose prescription according with tumor characteristics (histology, size, metabolic variables).

The use of two different RT techniques (non-coplanar fields and VMAT thereafter) could be considered a limit of our trial; as mentioned it was due to the long recruitment time. However, all the treatment plans were calculated by the same operator following the same constraints over the time thus ensuring homogeneity. Concerning plans optimization, our policy was to focus on dose homogeneity, using 5 mm multileaf collimator margins around the target volume and prescribing the dose to

the isocenter point as suggested by ICRU 62 and reported in Japanese studies.¹¹ After the implementation of the VMAT technique, we started following the suggestions of the ICRU 83 published in 2010 which is currently our standard for all intensity modulated plans. Nowadays, due to the enormous technological development in terms of organ motion control and accuracy of targeting, the most popular approach is to prescribe the dose to an isodose surface using tight multileaf collimator beam margin and obtaining both inhomogeneous intensified dose distributions within the target and rapid dose fall off outside it. This procedure was suggested by the SBRT report of the American Association of Physics in Medicine task Group 101⁴⁴ and in the

new trials ongoing in our department, we adopted these last guidelines along with ICRU 91 report ones.

In conclusion, in a prospective SBRT dose-escalation trial, the MTD of 50 Gy/10 Gy fraction and 35 Gy/7 Gy fraction were defined for primary and metastatic lesions and as boost after prior RT dose ≤ 50 Gy, respectively. Fractionated SBRT results in minimal acute and late toxicity. New indications for SBRT are currently being studied in oligoprogressive patients receiving targeted drugs or in combination with immunotherapy. The DESTROY-1 trial recruitment is still ongoing for arms where MTD has not yet been identified.

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