Higher Biologically Effective Dose Predicts Survival in SBRT of Pancreatic Cancer: A Multicentric Analysis (PAULA-1)

ALESSANDRA ARCELLI¹, ALESSANDRA GUIDO¹, MILLY BUWENGE¹,
NICOLA SIMONI², RENZO MAZZAROTTO², GABRIELLA MACCHIA³,
FRANCESCO DEODATO³, SAVINO CILLA⁴, PIERLUIGI BONOMO⁵, VALERIO SCOTTI⁶,
LILIANA BELGIOIA⁷, GIORGIO TOLENTO¹, FRANCESCO CELLINI⁸, ELISA GRASSI⁹,
MARIACRISTINA DI MARCO⁹, RICCARDO CASADEI¹⁰, ALESSIO G. MORGANTI¹ and SILVIA CAMMELLI¹

¹Radiation Oncology Center, Department of Experimental, Diagnostic and Specialty Medicine - DIMES, University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy;

²Radiotherapy Unit, Azienda Ospedaliera Universitaria, Verona, Italy;

³Radiotherapy Unit, 'Giovanni Paolo II' Foundation, Catholic University of Sacred Heart, Campobasso, Italy;

⁴Medical Physic Unit, 'Giovanni Paolo II' Foundation, Catholic University of Sacred Heart, Campobasso, Italy;

⁵Radiation Oncology Unit, Department of Experimental and Clinical Biomedical Sciences, Azienda Ospedaliero-Universitaria Careggi (AOUC), University of Florence, Florence, Italy;

⁶San Rossore Private Hospital, Pisa, Italy;

⁷Department of Radiotherapy, Policlinico San Martino, University of Genoa, Genoa, Italy;

⁸Fondazione Policlinico Universitario "A. Gemelli" IRCCS, UOC di Radioterapia Oncologica, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Rome, Italy;

⁹Oncology Unit, Department of Experimental, Diagnostic and Specialty Medicine - DIMES, University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy;

¹⁰Department of Medical and Surgical Sciences - DIMEC, University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy

Abstract. Aim: The purpose of the present multicentric study was to review stereotactic body radiotherapy (SBRT) with or without chemotherapy (CHT) experience in locally advanced pancreatic cancer (LAPC). Endpoints were overall survival (OS), local control (LC), and distant metastasis-free survival (DMFS). Several parameters' impact on these outcomes was assessed. Materials and Methods: Fifty-six patients with LAPC undergoing SBRT+/-CHT were included. SBRT median BED_{α/β10Gy} was 48.0 Gy (range=28.0-78.7). Survival curves were calculated by Kaplan-Meier method. A Cox regression model was fitted. Results: At a median follow-up of 15.0

months, 2-year OS, LC, DMFS were: 33.8% 55.4%, and 22.9%, respectively. Patients treated with BED_{α/β10Gy}≥48 Gy showed improved OS (p=0.020) and LC (p=0.024). At multivariate analysis, BED_{α/β10Gy}≥48 Gy was significantly associated to both higher OS (p=0.042) and LC (p=0.045), while post-SBRT CHT improved DMFS (p=0.003). Conclusion: SBRT proved to be tolerable and effective in LAPC. Moreover, BED_{α/β10Gy}≥48 Gy was significantly correlated with improved OS and LC.

Pancreatic cancer (Pca) is projected to become the second cancer killer in the United States by 2030 (1). Overall, 5-year survival in Pca patients is only 8% (2). Radical surgery achieving negative margins is the only treatment able to gain long-term survival (3, 4).

Unfortunately, only a small percentage of patients (around 20%) present with a resectable tumor at diagnosis, while 30-40% of them have unresectable locally advanced disease (5). Moreover, these patients represent a category with an intermediate prognosis between resectable and metastatic disease (6), with a median overall survival (OS) ranging from 9 to 11 months (5).

Nowadays, a therapeutic standard approach for Pca is missing and therefore the treatment is frequently institution

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Correspondence to: Milly Buwenge, MSc, Radiation Oncology Center, Department of Experimental, Diagnostic and Specialty Medicine - DIMES, University of Bologna, S. Orsola-Malpighi Hospital, Via Giuseppe Massarenti 9, 40138, Bologna, Italy. Tel: +39 0512143564, Fax: +39 0516364336, e-mail: mbuwenge@gmail.com

Key Words: Pancreatic cancer, stereotactic body radiotherapy, chemotherapy, dose effect.

dependent. Furthermore, robust evidence is lacking and guidelines are based on controversial studies and underpowered randomized trials (7).

Stereotactic body radiotherapy (SBRT) is an emerging radiotherapy (RT) technique based on high-precision image-guided delivery of ablative RT dose. SBRT allows a short overall treatment time (1 to 5 fractions) and optimal sparing of the adjacent Organs at Risk (OaRs) with reduced risk of toxicity (8). Moreover, compared to standard RT, the short duration of SBRT improves the integration with chemotherapy (CHT) while minimizing its interruptions or delays (7). Furthermore, it has the potential to overcome the intrinsic radiation-resistance of Pca due to the possibility to deliver high biologically effective doses (BED) (9). For all these reasons, SBRT is a promising therapeutic option for Pca (10, 11).

However, no phase III trials have been reported on SBRT in locally advanced pancreatic cancer (LAPC). Only a few mono- and multi-institutional, retrospective (12-14) or prospective studies (11, 15, 16) have been published with favourable preliminary results. Nevertheless, these analyses were generally performed on small and heterogeneous series (including not only LAPC) and reported partially the clinical outcomes (LC or OS).

Based on this background, we planned a retrospective analysis on a relatively large LAPC patient series to enrich the growing evidence of SBRT in this setting. Moreover, a detailed analysis of clinical outcomes [OS, LC, distant metastasis-free survival (DMFS) and toxicity] was performed. In addition, we studied the impact of both SBRT dose and CHT on OS and pattern of failure. The aim of this paper is to present the results of this analysis on SBRT in LAPC (PAULA-1: Pooled Analysis in Unresectable Locally Advanced pancreatic cancer).

Materials and Methods

Study design. We developed a large database on LAPC collecting clinical data of 434 patients from Italian centers on behalf of the Italian Association of Radiation Oncology (AIRO) Gastrointestinal Study Group. Patients could have been treated with all sequences and/or integrations of CHT and RT performed with various techniques. Patients with LAPC from six different institutions (Bologna, Verona, Campobasso, Agropoli, Florence, Genoa) treated with SBRT with or without CHT between January 2013 and March 2018 were selected from this database in order to perform this multicentric study.

Endpoints. Endpoints of this analysis were OS, LC, DMFS (all calculated from the date of treatment start), and toxicity. Our aim was also to assess the impact of several disease- and treatment-related parameters on the outcomes of patients.

Eligibility. Exclusion criteria included both metastatic disease and previous radical resection. All patients provided a written informed consent for the scientific use of their data. The study was approved by the institutional review boards of the participating centers.

Treatment. Patients were immobilized in supine position with a body frame system or a frameless system in one center using robotic SBRT. In 2 centers including the one using robotic SBRT, patients had 3 to 5 fiducial markers implanted into the tumor using endoscopic ultrasound guidance.

CT-simulation was performed in all centers with oral and intravenous contrast. In 3 centers, a 4-dimensional (4D) CT scan was carried out. Fusion of CT-simulation with fluorine-18-fluorodeoxyglucose positron emission tomography integrated with CT (18F-FDG PET/CT) or magnetic resonance imaging (MRI) was performed when available to improve gross tumor volume (GTV) and OaRs delineation. The center delivering robotic SBRT used a real time tumor tracking based on the implanted fiducials. In the other centers, abdominal compression was adopted for motion management in combination with daily kV cone beam CT.

The GTV was defined as the tumor visible on 3D CT-simulation. The clinical target volume (CTV) was defined as the GTV, while the planning target volume (PTV) encompassed the CTV with a 5 mm expansion. In case of delineation based on 4D CT, an internal target volume (ITV) was defined based on GTV position during the selected respiratory phases. In these cases, the ITV to PTV margin was 5 mm.

Treatment was delivered on daily basis with 3D conformal RT, intensity modulated radiation therapy (IMRT), helical IMRT, volumetric modulated arc therapy (VMAT), or a robotic device based on the institution. Thirty-seven patients were treated with a linear accelerator, 11 patients with a robotic unit, and 8 patients with helical tomotherapy. In most patients, prescription isodoses ranged from 95% to 100% to the PTV with 105% to 107% maximum dose to the PTV.

Follow-up. Patients were evaluated 15-20 days after SBRT, then every 3 months in the first 2 years and every 6 months thereafter. Patient evaluation included clinical examination, CA19.9 levels (U/ml), and imaging studies (mainly CT or ¹⁸F-FDG-PET). Patients evaluation was anticipated in case of reported symptoms.

Toxicity. Toxicity was retrospectively assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Acute toxicity was recorded during treatment and at first and second follow-up visits after SBRT. Any toxicity registered after three months from the end of SBRT was considered as late.

Statistical analysis. Descriptive statistics was used to report patient and treatment characteristics. Continuous variables were presented as median and range, while categorical variables were expressed as number and percentages. Survival functions were plotted using the Kaplan-Meier method (17) and compared by log-rank test (18). The parameters associated with significant differences at univariate analysis were entered in a multivariable Cox's proportional hazard model using a backward stepwise [Wald] strategy (19) (p -removal ≥ 0.10 ; p -addition < 0.10) in order to obtain a final model including only the subset of statistically significant variables. All tests were two-sided and a p -value < 0.05 was considered statistically significant. Statistical analysis was performed with IBM SPSS Version 22.0 (IBM Corp, Armonk, NY, USA).

In order to evaluate the dose effects across different fractionation schedules, the biologically effective dose assuming an α/β ratio of 10 Gy for Pca ($BED_{\alpha/\beta 10Gy}$) (20), was calculated based on the linear quadratic equation (21).

Table I. Univariate analysis of overall survival, local control, and distant metastasis-free survival.

Variable	Patients N (%)	6-month OS	1-year OS	2-year OS	Median OS	<i>p</i> -Value	6-month LC	1-year LC	2-year LC	Median LC	<i>p</i> -Value	6-month DMFS	1-year DMFS	2-year DMFS	Median DMFS	<i>p</i> -Value
Age (years)																
≤65	24 (42.8)	95.8	87.5	38.7	24.0	0.171	95.8	86.7	53.4	NR	0.164	82.9	56.0	0.0	15.0	0.665
>65	32 (57.2)	90.6	77.9	15.7	16.0		90.1	67.7	61.6	NR		87.4	55.8	41.8	13.0	
ECOG																
0	28 (50.0)	96.4	89.1	49.3	20.0	0.250	96.4	85.3	56.9	NE	0.026	92.7	58.9	NE	14.0	0.526
1	23 (41.0)	87.0	69.1	23.2	17.0		85.6	58.9	40.4	NE		73.7	52.7	22.6	13.0	
2	5 (9.0)	100.0	100.0	NE	15.0		100.0	100.0	100.0	NE		100.0	60.0	NE	13.0	
Tumor site																
Head	34 (60.6)	90.9	84.6	24.3	16.0	0.175	93.6	79.4	48.1	22.0	0.665	93.8	53.0	17.6	13.0	0.823
Body	19 (34.0)	94.7	73.7	0.0	20.0		88.8	71.1	63.9	NR		73.3	61.5	30.8	14.0	
Tail	3 (5.4)	100.0	100.0	100.0	29.0		100.0	66.7	66.7	NR		66.7	33.3	NE	8.0	
Tumor diameter (cm)																
≤3.9	28 (50.0)	100.0	92.9	29.1	17.0	0.790	96.4	76.8	76.8	NR	0.376	96.4	51.2	11.4	13.0	0.202
>3.9	25 (44.6)	84.0	68.0	26.3	24.0		86.5	72.1	42.7	22		75.2	61.1	26.2	22.0	
Unknown	3 (5.4)															
cT stage																
3	15 (23.2)	100.0	100.0	25.2	20.0	0.508	92.3	60.6	33.7	NE	0.067	84.6	38.5	NE	NE	0.113
4	41 (73.2)	90.2	75.2	30.7	20.0		92.2	80.6	60.4	NE		85.2	59.3	24.4	NE	
cN stage																
0	34 (60.7)	88.2	79.2	25.4	16.0	0.118	93.5	76.3	70.8	NR	0.583	81.9	46.3	24.6	12.0	0.537
1	22 (39.3)	100.0	86.4	21.8	24.0		90.9	76.3	0.0	22.0		90.9	68.2	0.0	16.0	
CA19.9 (U/ml)																
≤90	11 (19.7)	81.8	81.8	17.5	16.0	0.575	90.0	90.0	72.0	NR	0.481	90.0	60.0	30.0	16.0	0.843
>90	26 (46.4)	100.0	88.1	27.3	24.0		96.2	75.3	50.2	NR		80.8	63.7	20.9	15.0	
Unknown	19 (33.9)															
Chemotherapy																
No	15 (26.8)	80.0	58.7	NE	14	<0.001	92.3	59.3	NE	14	0.376	93.3	47.5	NE	12	0.010
Pre-SBRT	18 (32.1)	100.0	94.4	0.0	24		88.9	88.9	NE	NR		83.3	77.8	NE	NR	
Post-SBRT	10 (17.9)	90.0	80.0	60.0	NR		90.0	68.6	68.6	NR		90.0	57.1	42.9	13	
Pre- and post- SBRT	13 (23.2)	100.0	92.3	54.9	29		100.0	75.0	37.5	22		76.9	30.8	NE	10	
SBRT dose (Gy)																
<30	22 (39.3)	90.9	72.2	19.6	15.0	0.030	90.2	57.5	43.1	16.0	0.024	81.8	49.5	21.2	12.0	0.415
≥30	34 (60.7)	94.1	88.1	48.4	20.0		94.0	87.5	55.3	NR		88.1	59.8	25.7	14.0	
SBRT dose per fraction (Gy)																
≤6	41 (73.2)	92.7	77.6	46.8	20.0	0.198	97.3	85.9	64.4	NR	<0.001	90.0	59.3	25.5	14.0	0.098
>6	15 (26.8)	93.3	93.3	14.4	16.0		80.0	53.3	28.4	14.0		73.3	46.7	NE	10.0	
BED _{α/βGy10}																
<48	23 (41.0)	87.0	69.1	18.7	15.0	0.020	90.2	57.5	43.1	16.0	0.024	82.4	49.8	NE	12.0	0.447
≥48	33 (59.0)	97.0	90.8	49.9	20.0		93.9	87.4	55.2	NR		87.8	59.6	25.6	14.0	

OS: Overall survival; LC: local control; DMFS: distant metastasis-free survival; ECOG: Eastern Cooperative Oncology Group; cT stage: clinical tumor stage; cN stage: clinical nodal stage; NE: not evaluable; NR: not reached; SBRT: stereotactic body radiotherapy; BED: biologically effective dose. Statistically significant *p*-values are shown in bold.

Results

Patients and treatment characteristics. Based on the selection criteria, 56 patients [Male/Female 31/25 (55.3%/44.7%)] with SBRT+/-CHT were included in this analysis. ECOG was 0, 1, and 2 in 28 (50.0%), 23

(41.0%), and 5 (9.0%) of patients, respectively (Table I). Tumor sites were head 34 (60.6%), body 19 (34.0%), tail 3 (5.4%) (Table I). Median age and median follow-up were 68 years (range=36-89) and 15.0 months (range=3.0-70.0), respectively. Median tumour diameter was 3.9 cm (range=1.2-8.7).

CHT was administered to 18 (32.1%) patients in pre-SBRT setting, to 10 patients after SBRT (17.9%), and to 13 (23.2%) patients in both pre- and post-SBRT setting. Fifteen patients (26.8%) underwent SBRT alone (Table I). Pre- and post-SBRT CHT regimens were mainly based on gemcitabine (43.5%) or gemcitabine plus nab-paclitaxel (38.7%), respectively.

SBRT treatments were delivered using VMAT (33.9%), IMRT (26.8%), helical IMRT (14.3%), robotic device (19.6%), or with 3D conformal RT (5.4%). Median total dose was 30.0 Gy (range=18.0-45.0) and median dose per fraction was 6.0 Gy (range=4.0-10.0). Median $BED_{\alpha/\beta 10Gy}$ was 48.0 Gy (range=28.0-78.7).

Local control. Six-month, 1-, and 2-year LC were: 92.5%, 76.3%, and 55.4%, respectively. Median LC was not reached. At univariate analysis, patients with ECOG 2 ($p=0.026$), treated with a total SBRT dose ≥ 30 Gy ($p=0.024$), with a fractionation dose ≤ 6 Gy ($p<0.001$), and with a computed $BED_{\alpha/\beta 10Gy} \geq 48$ Gy ($p=0.024$) showed a significantly improved LC (Table I).

Due to the intrinsic correlation between $BED_{\alpha/\beta 10Gy}$ and fractionation, we performed 2 separate multivariate analyses including SBRT dose/fraction in 1 model and $BED_{\alpha/\beta 10Gy}$ in the other model. This was due to the statistically significant correlation of LC with both parameters at univariate analysis. Both $BED_{\alpha/\beta 10Gy} \geq 48$ Gy (HR=0.34, 95% CI=0.12-0.97, $p=0.045$) and dose per fraction >6 Gy (HR=4.76, 95% CI=1.69-13.44, $p=0.003$) remained independently associated with LC in these separate multivariate analyses. Their effect was opposite: $BED_{\alpha/\beta 10Gy} \geq 48$ Gy resulted to be a significant and independent predictor of improved LC, while fractionation dose >6 Gy was correlated to an increased risk of recurrence. The other covariates significantly influencing LC at univariate analysis (cT stage and ECOG) were also included in the multivariate analyses. Neither ECOG (HR=1.80, 95% CI=0.55-5.85, $p=0.326$ and HR=1.38, 95% CI=0.41-4.60, $p=0.599$) nor cT stage (HR=0.63, 95% CI=0.21-1.90, $p=0.419$ and HR=1.09, 95% CI=0.30-3.91, $p=0.886$) remained significantly correlated to LC either in the first model including $BED_{\alpha/\beta 10Gy}$, or in the second model including fractionation dose, respectively.

Distant metastasis-free survival. Median, 6-month, 1-, and 2-year DMFS were: 14.0 months, 85.5%, 55.8%, and 22.9%, respectively. At univariate analysis, patients undergoing pre-SBRT CHT developed metastases later compared to patients undergoing SBRT alone or combined with post-SBRT CHT or with both post-SBRT and pre-SBRT CHT (Table I). Conversely, at multivariable analysis, only post-SBRT CHT (HR=0.22, 95% CI=0.08-0.59, $p=0.003$) was correlated with improved DMFS.

Figure 1. Overall survival stratifying patients based on median biologically effective dose assuming an α/β ratio of 10 Gy for pancreatic cancer ($BED_{\alpha/\beta 10Gy}$).

Overall survival. Median, 6-month, 1-, and 2-year OS were: 19.0 months, 92.9%, 81.9%, and 33.8%, respectively. At univariate analysis, an improved OS was recorded in patients receiving pre- and post-SBRT CHT ($p<0.001$), in patients treated with a total SBRT dose ≥ 30 Gy ($p=0.030$), and with a computed $BED_{\alpha/\beta 10Gy} \geq 48$ Gy ($p=0.020$) (Table I).

Even at multivariate analysis, the delivery of a $BED_{\alpha/\beta 10Gy} \geq 48$ Gy (HR=0.44, 95% CI=0.20-0.97, $p=0.042$) was significantly correlated with improved OS. Median OS was 15.0 months (95% CI=14.0-16.0) in patients receiving <48 Gy $BED_{\alpha/\beta 10Gy}$ versus 20.0 months (95% CI=17.8-22.1) in those with ≥ 48 Gy $BED_{\alpha/\beta 10Gy}$ (Figure 1). The multivariable analysis also showed a significant advantage in terms of OS in patients treated with SBRT plus CHT, administered either as post-SBRT (HR=0.15, 95% CI=0.04-0.60, $p=0.007$), or pre-SBRT (HR=0.30, 95% CI=0.12-0.78, $p=0.014$), or combined pre- and post-SBRT setting (HR=0.20, 95% CI=0.07-0.57, $p=0.003$), compared to those treated with SBRT alone.

The univariate sub-analysis of the impact of $BED_{\alpha/\beta 10Gy}$ on OS in different patient subsets is reported in Table II. The positive impact of $BED_{\alpha/\beta 10Gy} \geq 48$ Gy was recorded in patients: older than 65 years ($p<0.001$), females ($p=0.016$), with CA19.9 levels ≥ 90 U/ml ($p=0.003$), with tumor in the pancreatic body ($p<0.001$), with tumor diameter ≥ 3.9 cm ($p=0.016$), with cT4 stage ($p=0.003$), and with cN0 stage ($p=0.036$).

Table II. Univariate sub-analysis of all predictor values of 6-month, 1-, 2-year overall survival, and median survival time. Data are stratified for median BED_{α/β10Gy} (<48 Gy vs ≥48 Gy).

Variable	Patients N	Overall survival								p-Value
		6-month (%)		1-year (%)		2-year (%)		Median (months)		
BED _{α/β10Gy}		<48	≥48	<48	≥48	<48	≥48	<48	≥48	
Age (years)										
≤65	24	100.0	93.3	77.8	93.3	38.9	47.9	24	20	0.714
>65	32	78.6	100.0	64.3	88.5	NE	26.1	14	24	<0.001
ECOG										
0	28	100.0	95.7	80.0	91.3	20.0	56.8	15	NR	0.097
1	23	78.6	100.0	56.3	88.9	23.4	21.2	13	20	0.090
2	5	100.0	100.0	100.0	100.0	NE	NE	15	15	0.414
Gender										
Male	31	92.9	94.1	71.4	88.2	19.8	0.0	15	24	0.108
Female	25	77.8	100.0	64.8	93.3	16.2	27.7	14	20	0.016
CA19.9 (U/ml)										
<90	11	80.0	83.3	80.0	83.3	20.0	27.8	16	17	0.914
>90	26	88.9	100.0	65.8	92.4	19.7	27.6	15	24	0.003
Tumor Site										
Head	34	86.7	94.4	79.4	88.9	11.2	44.4	15	19	0.083
Body	19	83.3	100.0	33.3	92.3	0.0	0.0	8	21	<0.001
Tail	3	100.0	100.0	100.0	100.0	100.0	100.0	NR	NR	NE
Tumor diameter (cm)										
<3.9	28	100.0	100.0	100.0	94.1	25.7	31.6	16	19	0.437
≥3.9	25	80.0	93.8	53.3	87.5	15.2	34.4	14	24	0.016
cT-stage										
3	15	100.0	100.0	100.0	100.0	28.6	0.0	16	20	0.800
4	41	78.6	96.3	48.2	88.7	25.7	28.3	11	24	0.003
cN-stage										
N0	34	78.6	95.0	64.3	89.7	18.4	28.5	15	19	0.036
N+	22	100.0	100.0	77.8	92.3	20.0	0.0	15	24	0.101
Chemotherapy										
No	15	75.0	85.7	60.0	60.0	NE	NE	13	14	0.572
Pre- SBRT	18	100.0	100.0	80.0	100.0	0.0	0.0	16	24	0.072
Post- SBRT	10	83.3	100.0	66.7	100.0	33.3	0.0	NE	NE	0.117
Pre- & Post- SBRT	13	100.0	100.0	75.0	100.0	50.0	NE	15	NR	0.587

BED: Biologically effective dose; cT: clinical tumor stage; cN: clinical nodal stage; ECOG: Eastern Cooperative Oncology Group; NE: not evaluable; NR: not reached; SBRT: stereotactic body radiotherapy. Statistically significant *p*-values are shown in bold.

Toxicity. Gastrointestinal acute toxicity rates were as follows: G0: 78.5%, G1: 19.6%, G2: 1.9%, G3: 0.0%. No cases of G1-G2 gastrointestinal late toxicity were reported. However, one case of G3 gastrointestinal late toxicity (2.5%) represented by an episode of upper gastrointestinal bleeding was recorded.

Discussion

This multicentric retrospective study represents one of the largest series on SBRT with or without CHT in LAPC, comparable in terms of sample size to only few other retrospective (12, 14, 22, 23) and prospective series (16). Furthermore, to the best of our knowledge, this is the first

study evaluating several outcomes, including pattern of failure (LC, DMFS), and identifying a BED_{α/β10Gy} cut-off significantly predicting both LC and OS.

Moreover, our cohort is homogenous in terms of tumor stage. In fact, only LAPC patients were included, while the majority of the previous reports included recurrences, metastatic disease, borderline resectable disease, or resectable disease pooled together (11, 13, 24, 25).

Due to its retrospective and multicentric nature, this study has some limitations. Particularly, treatment planning and RT delivery techniques were different between centres. Even CHT was not uniform in terms of timing and drugs, thus reflecting the lack of treatment standards in LAPC (7). However, this data inhomogeneity allowed us to compare

different SBRT doses and treatment integrations in terms of CHT timing.

Our results showed a significantly positive impact of higher SBRT $BED_{\alpha/\beta 10Gy}$ both on LC and OS. This data may suggest that achieving higher LC rates may result in improved OS as recorded by Comito *et al.* (26). Furthermore, the positive correlation between $BED_{\alpha/\beta 10Gy}$ and LC that was recorded here confirmed the results of 2 systematic literature reviews (27, 28).

Moreover, the positive impact of relatively low dose/fraction on LC is consistent with the observation of a positive effect of a higher number of fractions on this endpoint (28). These results seem to suggest that the α/β ratio of Pca is particularly high, probably above 10 Gy.

The impact of $BED_{\alpha/\beta 10Gy}$ on OS was investigated in previous reports with negative results. In a retrospective mono-institutional study on LAPC SBRT plus CHT, $BED_{\alpha/\beta 10Gy}$ was not correlated with OS (24). Similar results were reported in a systematic literature review (27). On the contrary, our study demonstrated that the delivery of $BED_{\alpha/\beta 10Gy} \geq 48$ Gy was significantly correlated with improved OS. This discrepancy might derive from the different $BED_{\alpha/\beta 10Gy}$ cut-off used to stratify patients in the different analyses. In fact, we used the relatively low value of 48 Gy, while both studies cited above used higher cut-off values (24, 27).

Furthermore, Table II shows the significant impact of higher $BED_{\alpha/\beta 10Gy}$ on OS in different patient subsets, including those with unfavourable prognostic factors (tumor diameter ≥ 3.9 cm, cT4, CA19.9 ≥ 90 U/ml). However, the lack of statistical significance in some subgroups can be simply attributed to the small sample size of some patient subsets.

As expected, even CHT was significantly correlated with improved OS. This result confirms a similar advantage reported in other studies (11, 13, 16, 22, 24, 29, 30). CHT resulted to be an independent significant predictor of improved OS regardless of different settings. Post-SBRT CHT demonstrated a prolonged DMFS. However, this data might be partially due to the prescription of post-SBRT CHT only to patients without early progressive disease after SBRT.

Our results in terms of 1-year LC (76.3%) are similar to those of the previously cited systematic review of Petrelli and colleagues (72.3%) (28). Moreover, our results in terms of median OS (19.0 months) are similar to those of the aforementioned review (17.0 months) (28). Finally, gastrointestinal acute and late toxicity recorded in the current study are comparable with other retrospective reports on SBRT (13, 31) and with the review of Petrelli and coworkers (28).

Before the introduction of SBRT, chemoradiation with conventional fractionation with or without CHT represented the traditional RT modality in LAPC. If we compare our results (median OS: 19.0 months) with those based on chemoradiation plus CHT from 2 relatively recent trials (median OS: 13.4-15.2

months) (32, 33), the results of the SBRT are at least comparable to those of the traditional treatment.

Our report showed wide inhomogeneity in SBRT of LAPC (in terms of dose, fractionation, and technique), probably attributable to the lack of guidelines in this setting. However, data about tolerability, pain relief (34), and outcomes suggest that SBRT can be considered as a treatment option in clinical practice.

The present series and other studies showed a positive impact of the SBRT plus CHT on LAPC. Therefore, SBRT could be always combined with CHT if clinically feasible. Prospective trials aiming to identify the optimal timing of SBRT and CHT combination are needed. Moreover, considering the contradictory results regarding dose and fractionation impact among the available series, further studies on this issue are justified. In particular, the significantly improved LC in patients treated with higher total doses and in the ones receiving lower dose/fraction seems to suggest the opportunity to test prolonged treatment schedules (10-15 fractions) compared to the currently used protocols (1-5 fractions). Finally, testing advanced on-board imaging systems with the aim of reducing the risk of toxicity to allow high SBRT doses delivery seems justified (35). Currently, we are running a multicentric phase II trial in LAPC patients to evaluate the effect of neoadjuvant SBRT followed by CHT on resectability (IRENE-1: Improving Resectability in pancreatic Neoplasm: ClinicalTrials.gov identifier NCT03460925) (36).

Conflicts of Interest

The Authors have no actual or potential conflicts of interest regarding this paper.

Authors' Contributions

Conceptions and design were performed by AGM, AA, AG, MB, and SiC. AA, GM, FD, PB, VS, LB, GT, EG and MDM contributed to data collection. Analysis and interpretation of data were performed by AA, AGM, MB, NS, RM and FD. AA, AGM, MB, SiC and AG contributed to manuscript writing, and NS, RM, FC, PB, VS, LB, GM and SC to the critical review of the manuscript. All Authors read and approved the final manuscript and gave consent to publication

Acknowledgements

The Authors sincerely acknowledge AIRO (Italian Association of Radiation Oncology) Group for Gastrointestinal Cancer for supporting the study.

References

- Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM and Matrisian LM: Projecting cancer incidence and deaths

- to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 74(11): 2913-2921, 2014. PMID: 24840647. DOI: 10.1158/0008-5472.CAN-14-0155
- 2 Siegel RL, Miller KD and Jemal A: Cancer statistics, 2018. *CA Cancer J Clin* 68(11): 7-30, 2018. PMID: 29313949. DOI: 10.3322/caac.21442
- 3 Wagner M, Redaelli C Lietz M, Seiler CA, Friess H and Büchler MW: Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. *Br J Surg* 91(5): 586-594, 2004. PMID: 15122610. DOI: 10.1002/bjs.4484
- 4 Li D, Xie K, Wolff R and Abbruzzese JL: Pancreatic cancer. *Lancet* 363(9414): 1049-1057, 2004. PMID: 15051286. DOI: 10.1016/S0140-6736(04)15841-15848
- 5 Hidalgo M: Pancreatic cancer. *N Engl J Med* 362(17): 1605-1617, 2010. PMID: 20427809 DOI: 10.1056/NEJMra0901557
- 6 Willett CG, Czito BG, Bendell JC and Ryan DP: Locally advanced pancreatic cancer. *J Clin Oncol* 23(20): 4538-4544, 2005. PMID: 16002845. DOI: 10.1200/JCO.2005.23.911
- 7 Loehrer PJ Sr, Feng Y, Cardenes H, Wagner L, Brell JM, Cella D, Flynn P, Ramanathan RK, Crane CH, Alberts SR and Benson AB 3rd: Gemcitabine alone *versus* gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. *J Clin Oncol* 29(31): 4105-4112, 2011. PMID: 21969502. DOI: 10.1200/JCO.2011.34.8904
- 8 Potters L, Kavanagh B, Galvin JM, Hevezi JM, Janjan NA, Larson DA, Mehta MP, Ryu S, Steinberg M, Timmerman R, Welsh JS and Rosenthal SA: American Society for Therapeutic Radiology and Oncology; American College of Radiology. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 76(2): 326-332, 2010. PMID: 20117285. DOI: 10.1016/j.ijrobp.2009.09.042
- 9 Swaminath A and Chu W: Stereotactic body radiotherapy for the treatment of medically inoperable primary renal cell carcinoma: Current evidence and future directions. *Can Urol Assoc J* 9(7-8): 275-280, 2015. PMID: 26316914. DOI: 10.5489/cuaj.2900
- 10 Schellenberg D, Goodman KA, Lee F, Chang S, Kuo T, Ford JM, Fisher GA, Quon A, Desser TS, Norton J, Greco R, Yang GP and Koong AC: Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 72(3): 678-686, 2008. PMID: 18395362. DOI: 10.1016/j.ijrobp.2008.01.051
- 11 Gurka MK, Collins SP, Slack R, Tse G, Charabaty A, Ley L, Berzcel L, Lei S, Suy S, Haddad N, Jha R, Johnson CD, Jackson P, Marshall JL and Pishvaian MJ: Stereotactic body radiation therapy with concurrent full-dose gemcitabine for locally advanced pancreatic cancer: a pilot trial demonstrating safety. *Radiat Oncol* 8: 44, 2013. PMID: 23452509. DOI: 10.1186/1748-717X-8-44
- 12 Song Y, Yuan Z, Li F, Dong Y, Zhuang H, Wang J, Chen H and Wang P: Analysis of clinical efficacy of CyberKnife® treatment for locally advanced pancreatic cancer. *Onco Targets Ther* 8: 1427-1431, 2015. PMID: 26109866. DOI: 10.2147/OTT.S81939
- 13 Moningi S, Dholakia AS, Raman SP, Blackford A, Cameron JL, Le DT, De Jesus-Acosta AM, Hacker-Prietz A, Rosati LM, Assadi RK, Dipasquale S, Pawlik TM, Zheng L, Weiss MJ, Laheru DA, Wolfgang CL and Herman JM: The role of stereotactic body radiation therapy for pancreatic cancer: A single-institution experience. *Ann Surg Oncol* 22(7): 2352-2358, 2015. PMID: 25564157. DOI: 10.1245/s10434-014-4274-5
- 14 Ryan JF, Rosati LM, Groot VP, Le DT, Zheng L, Laheru DA, Shin EJ, Jackson J, Moore J, Narang AK and Herman JM: Stereotactic body radiation therapy for palliative management of pancreatic adenocarcinoma in elderly and medically inoperable patients. *Oncotarget* 9(23): 16427-16436, 2018. PMID: 29662656. DOI: 10.18632/oncotarget.24713
- 15 Tozzi A, Comito T, Alongi F, Navarra P, Iftode C, Mancosu P, Reggiori G, Clerici E, Rimassa L, Zerbi A, Fogliata A, Cozzi L, Tomatis S and Scorsetti M: SBRT in unresectable advanced pancreatic cancer: preliminary results of a mono-institutional experience. *Radiat Oncol* 8: 148, 2013. PMID: 23799996. DOI: 10.1186/1748-717X-8-148
- 16 Herman JM, Chang DT, Goodman KA, Dholakia AS, Raman SP, Hacker-Prietz A, Iacobuzio-Donahue CA, Griffith ME, Pawlik TM, Pai JS, O'Reilly E, Fisher GA, Wild AT, Rosati LM, Zheng L, Wolfgang CL, Laheru DA, Columbo LA, Sugar EA and Koong AC: Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. *Cancer* 121(7): 1128-1137, 2015. PMID: 25538019. DOI: 10.1002/cncr.29161
- 17 Kaplan EL and Meier P: Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53: 457-481, 1958. DOI: 10.2307/2281868
- 18 Peto R and Peto J: Asymptotically efficient rank invariant procedures. *J R Statist Soc* 135: 185-207, 1972. DOI: 10.2307/2344317
- 19 Cox DR: Regression models and life tables (with discussion). *J R Statist Soc* 74: 187-220, 1972
- 20 Fowler JF, Tomé WA, Fenwick JD and Mehta MP: A challenge to traditional radiation oncology. *Int J Radiat Oncol Biol Phys* 60(4): 1241-1256, 2004. PMID: 15519797. DOI: 10.1016/j.ijrobp.2004.07.691
- 21 Yaes RJ, Patel P and Maruyama Y: On using the linear-quadratic model in daily clinical practice. *Int J Radiat Oncol Biol Phys* 20(6): 1353-1362, 1991. PMID: 2045309. DOI: 10.1016/0360-3016(91)90249-4
- 22 Mellon EA, Hoffe SE, Springett GM, Frakes JM, Strom TJ, Hodul PJ, Malafa MP, Chuong MD and Shridhar R: Long-term outcomes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma. *Acta Oncol* 54(7): 979-985, 2015. PMID: 25734581. DOI: 10.3109/0284186X.2015.1004367
- 23 Jung J, Yoon SM, Park JH, Seo DW, Lee SS, Kim MH, Lee SK, Park DH, Song TJ, Ryoo BY, Chang HM, Kim KP, Yoo C, Jeong JH, Kim SC, Hwang DW, Lee JH, Song KB, Jo YY, Park J and Kim JH: Stereotactic body radiation therapy for locally advanced pancreatic cancer. *PLoS One* 14(4): e0214970, 2019. PMID: 30978229. DOI: 10.1371/journal.pone.0214970
- 24 Pollom EL, Alagappan M, von Eyben R, Kunz PL, Fisher GA, Ford JA, Poultsides GA, Visser BC, Norton JA, Kamaya A, Cox VL, Columbo LA, Koong AC and Chang DT: Single- *versus* multifraction stereotactic body radiation therapy for pancreatic adenocarcinoma: outcomes and toxicity. *Int J Radiat Oncol Biol Phys* 90(4): 918-925, 2014. PMID: 25585785. DOI: 10.1016/j.ijrobp.2014.06.066
- 25 Rwigyema JC, Parikh SD, Heron DE, Howell M, Zeh H, Moser AJ, Bahary N, Quinn A and Burton SA: Stereotactic body radiotherapy in the treatment of advanced adenocarcinoma of the

- pancreas. *Am J Clin Oncol* 34(1): 63-69, 2011. PMID: 20308870. DOI: 10.1097/COC.0b013e3181d270b4
- 26 Comito T, Cozzi L, Zerbi A, Franzese C, Clerici E, Tozzi A, Iftode C, Navarria P, D'Agostino G, Fogliata A, Mancosu P, Tomatis S, Carnaghi C, Personeni N, Santoro A and Scorsetti M: Clinical results of stereotactic body radiotherapy (SBRT) in the treatment of isolated local recurrence of pancreatic cancer after R0 surgery: A retrospective study. *Eur J Surg Oncol* 43(4): 735-742, 2017. PMID: 28131670. DOI: 10.1016/j.ejso.2016.12.012
- 27 Brunner TB, Nestle U, Grosu AL and Partridge M: SBRT in pancreatic cancer: what is the therapeutic window? *Radiother Oncol* 114(1): 109-116, 2015. PMID: 25466369. DOI:10.1016/j.radonc.2014.10.015
- 28 Petrelli F, Comito T, Ghidini A, Torri V, Scorsetti M and Barni S: Stereotactic body radiation therapy for locally advanced pancreatic cancer: A systematic review and pooled analysis of 19 trials. *Int J Radiat Oncol Biol Phys* 97(2): 313-322, 2017. PMID: 28068239. DOI:10.1016/j.ijrobp.2016.10.030
- 29 Goyal K, Einstein D, Ibarra RA, Yao M, Kunos C, Ellis R, Brindle J, Singh D, Hardacre J, Zhang Y, Fabians J, Funkhouser G, Machtay M and Sanabria JR: Stereotactic body radiation therapy for nonresectable tumors of the pancreas. *J Surg Res* 174: 319-325, 2012. PMID: 21937061. DOI: 10.1016/j.jss.2011.07.044
- 30 Rajagopalan MS, Heron DE, Wegner RE, Zeh HJ, Bahary N, Krasinskas AM, Lembersky B, Brand R, Moser AJ, Quinn AE and Burton SA: Pathologic response with neoadjuvant chemotherapy and stereotactic body radiotherapy for borderline resectable and locally-advanced pancreatic cancer. *Radiat Oncol* 8: 254, 2013. PMID: 24175982. DOI: 10.1186/1748-717X-8-254
- 31 Mahadevan A, Miksad R, Goldstein M, Sullivan R, Bullock A, Buchbinder E, Pleskow D, Sawhney M, Kent T, Vollmer C and Callery M: Induction gemcitabine and stereotactic body radiotherapy for locally advanced nonmetastatic pancreas cancer. *Int J Radiat Oncol Biol Phys* 81(4): 615-622, 2011. PMID: 21658854. DOI: 10.1016/j.ijrobp.2011.04.045
- 32 Mukherjee S, Hurt CN, Bridgewater J, Falk S, Cummins S, Wasan H, Crosby T, Jephcott C, Roy R, Radhakrishna G, McDonald A, Ray R, Joseph G, Staffurth J, Abrams RA, Griffiths G and Maughan T: Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. *Lancet Oncol* 14(4): 317-326, 2013. PMID: 23474363. DOI: 10.1016/S1470-2045(13)70021-4
- 33 Hammel P, Huguet F, van Laethem JL, Goldstein D, Glimelius B, Artru P, Borbath I, Bouché O, Shannon J, André T, Mineur L, Chibaudel B, Bonnetain F, Louvet C and LAP07 Trial Group: Effect of chemoradiotherapy vs. chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: The LAP07 randomized clinical trial. *JAMA* 315(17): 1844-1853, 2016. PMID: 27139057. DOI: 10.1001/jama.2016.4324
- 34 Buwenge M, Macchia G, Arcelli A, Frakulli R, Fuccio L, Guerri S, Grassi E, Cammelli S, Cellini F and Morganti AG: Stereotactic radiotherapy of pancreatic cancer: a systematic review on pain relief. *J Pain Res* 11: 2169-2178, 2018. PMID: 30323651. DOI: 10.2147/JPR.S167994
- 35 Deodato F, Macchia G, Cilla S, Ianiro A, Sallustio G, Cammelli S, Buwenge M, Mattiucci GC, Valentini V and Morganti AG: Dose escalation in extracranial stereotactic ablative radiotherapy (DESTROY-1): A multiarm Phase I trial. *Br J Radiol* 92(1094): 20180422, 2019. PMID: 30325662. DOI: 10.1259/bjr.20180422
- 36 Improving REsectability in Pancreatic NEoplasms (IRENE) ClinicalTrials.gov U.S. National library of Medicine. Available at: <https://clinicaltrials.gov/ct2/show/NCT03460925>. Last accessed on 10 November 2019

Received November 21, 2019

Revised December 11, 2019

Accepted December 12, 2019