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OUTCOME ANALYSIS OF PREDICTORS IN LOCALLY ADVANCED PANCREATIC CANCER

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Sommario

Preface **4**
Abstract **6**
PAULA-1 Higher Biologically Effective Dose Predicts Survival in SBRT of Pancreatic Cancer: A Multicentric Analysis **7**
ABSTRACT 7
INTRODUCTION 8
MATERIALS AND METHODS 9
RESULTS 11
DISCUSSION 14
CONCLUSIONS 16
REFERENCES 17
TABLES 23
FIGURE LEGENDS 26
PAULA-2 Stereotactic body radiotherapy versus conventionally fractionated chemoradiation in locally advanced pancreatic cancer: a multicenter case-control study **28**
ABSTRACT 28
INTRODUCTION 30
MATERIALS AND METHODS 31
RESULTS 33
DISCUSSION 34
CONCLUSIONS 36
REFERENCES 38
TABLES 41
FIGURE LEGENDS 44
PAULA-3 Outcome analysis of different therapeutic option in locally advanced pancreatic cancer: a predictive model from a multicenter study **48**
ABSTRACT 48
INTRODUCTION 50
MATERIALS AND METHODS 51
RESULTS 52
DISCUSSION 54
CONCLUSIONS 57
REFERENCES 58
TABLES 62
FIGURE LEGENDS 65

Preface

The research presented in the first two chapters of the thesis are based on prior publications. These manuscripts have been obviously published during my PhD course, in particular during 2020. In case of the third chapter, prior works are only mentioned in passing, and data have not been published yet. Results presented in this thesis come from sharing data with many Radiation Oncologist colleagues from all around Italy. Conceptions and design are naturally not only of my own. Analysis, interpretation of results, and conceptualization had been processed with the collaboration of my tutor Alessio Giuseppe Morganti, and with my colleagues Milly Buwenge and Giuseppe Tarantino.

In particular, data presented in the fisrt two chapter have been adapted from these two scientific manuscripts:

1 *Arcelli A, Guido A, Buwenge M, Simoni N, Mazzarotto R, Macchia G, Deodato F, Cilla S, Bonomo P, Scotti V, Belgioia L, Tolento G, Cellini F, Grassi E, Di Marco M, Casadei R, Morganti AG, Cammelli S. Higher Biologically Effective Dose Predicts Survival in SBRT of Pancreatic Cancer: A Multicentric Analysis (PAULA-1). Anticancer Res. 2020;40(1):465-472. doi:10.21873/anticanres.13975*

2 *Arcelli A, Buwenge M, Macchia G, Bertini F, Guido A, Deodato F, Cilla S, Scotti V, Rosetto Me, Djan I, Parisi S, Mattiucci Gc, Cellini F, Fiore M, Bonomo P, Belgioia L, Niespolo Rm, Gabriele P, Di Marco M, Simoni N, Mazzarotto R, Morganti AG; the AIRO (Italian Association of Radiation Oncology and Clinical Oncology) Gastrointestinal Study Group. Stereotactic body radiotherapy vs conventionally fractionated chemoradiation in locally advanced pancreatic cancer: A multicenter case-control study (PAULA-1). Cancer Med. 2020;9(21):7879-7887. doi:10.1002/cam4.3330*

Abstract

Guidelines report a wide range of options in locally advanced pancreatic cancer (LAPC): definitive chemotherapy or chemoradiotherapy or the emerging stereotactic body radiotherapy (SBRT) (+/- chemotherapy). On behalf of the AIRO (Italian Association of Radiation Oncology and Clinical Oncology) Gastrointestinal Study Group, we collected retrospective clinical data on 419 LAPC from 15 Italian centers. The study protocol (PAULA-1: Pooled Analysis in Unresectable Locally Advanced pancreatic cancer) was approved by institutional review board of S. Orsola-Malpighi Hospital (201/2015/O/OssN). From this large database we performed tree different studies. The first was a retrospective study about 56 LAPC treated with SBRT at a median biologically equivalent dose of 48 Gy +/- chemotherapy. We demonstrated a statistically significant impact of biologically equivalent dose based on an α/β ratio of 10Gy $\geq$ 48Gy for local control (LC) (p: 0.045) and overall survival (p: 0.042) in LAPC. The second was a retrospective matched-cohort case-control study comparing SBRT (40 patients) and chemoradiation (40 patients) in LAPC in terms of different endpoints. Our findings suggested an equivalence in terms of most outcomes among the two treatments and an advantage of SBRT in terms of LC (p: 0.017). The third study was a retrospective comparison of definitive chemotherapy, chemoradiotherapy and SBRT (+/- chemotherapy) in terms of different outcomes in LAPC. A predictive model for LC in LAPC was also developed reaching an AUC of 68% (CI 58,7%-77,4%). SBRT treatment emerged as a positive predictive factor for improved LC.

Findings deriving from our three studies suggest that SBRT is comparable to standard of care (definitive chemotherapy and chemoradiotherapy) in terms of outcomes. SBRT seems to be an emerging therapeutic option in LAPC significantly improving local control. Furthermore, we have shown the potential of a predictive model for LC. Randomized trials are needed to compare these different therapeutic options in LAPC.

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

ABSTRACT

Aim: To review a multicentric stereotactic body radiotherapy (SBRT) +/- 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 $BED_{\alpha/\beta 10Gy}$ 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 $BED_{\alpha/\beta 10Gy} \geq 48$ Gy showed improved OS (p: 0.020) and LC (p: 0.024). At multivariate analysis, $BED_{\alpha/\beta 10Gy} \geq 48$ 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).

Conclusions: SBRT resulted tolerable and effective in LAPC. Moreover, $BED_{\alpha/\beta 10Gy} \geq 48$ Gy was significantly correlated with improved OS and LC.

INTRODUCTION

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 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 419 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 (^{18}F-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% to107% 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 ^{18}F-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).

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 $BED_{\alpha/\beta 10Gy}$ ≥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 $BED_{\alpha/\beta 10Gy}$ ≥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: $BED_{\alpha/\beta 10Gy}$ ≥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.

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 $BED_{\alpha/\beta 10Gy}$ ≥ 48 Gy (*p*=0.020) (Table I).

Even at multivariate analysis, the delivery of a $BED_{\alpha/\beta 10Gy}$ ≥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 $BED_{\alpha/\beta 10Gy}$ ≥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).

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 $BED_{\alpha/\beta 10Gy}$ 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.

CONCLUSIONS

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).

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TABLES

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

Variable	Value	Patients N (%)	6-month OS	1-year OS	2-year OS	Median OS	*p*-Values	6-month LC	1-year LC	2-year LC	Median LC	*p*-Values	6-month DMFS	1-year DMFS	2-year DMFS	Median DMFS	*p*-Values
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	
$BED_{\alpha/\beta Gy10}$	< 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

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 $BED_{\alpha/\beta 10Gy}$ (< 48 Gy vs ≥ 48 Gy).

Variable	Value	No patients	Overall survival								*p*-Value
			6 month (%)		1-year (%)		2-year (%)		Median (months)		
$BED_{\alpha/\beta 10Gy}$			< 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

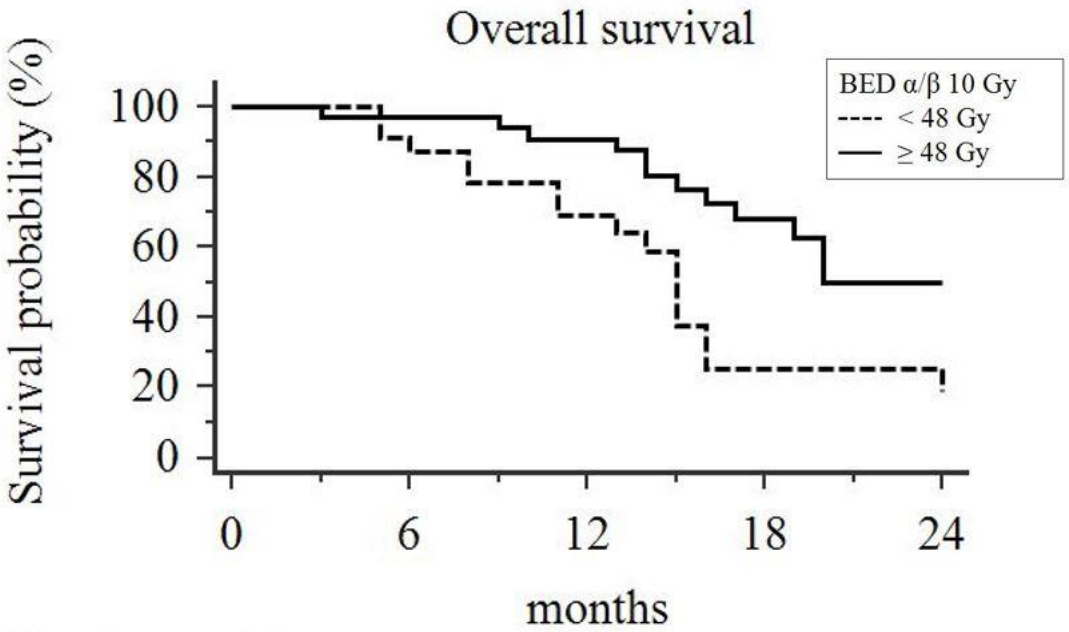
BED: biologically effective dose; cT: clinical tumor stage; cN: clinical nodal stage; ECOG: Eastern Cooperative Oncology Group; NE: not evaluable; NR: not reached; SBRT: stereotactic body radiotherapy.

Statistically significant *p*-values are shown in bold.

FIGURE LEGENDS

Figure 1: Overall survival stratifying patients based on median biologically effective dose (BED) $\alpha/\beta 10Gy$.

Figure 1:



Number at risk

< 48 Gy	23	20	14	4	2
≥ 48 Gy	33	32	27	12	1

PAULA-2 Stereotactic body radiotherapy versus conventionally fractionated chemoradiation in locally advanced pancreatic cancer: a multicenter case-control study

ABSTRACT

Aim: Conventionally fractionated chemoradiation (CRT) or chemotherapy (CHT) are considered as standard options in locally advanced pancreatic cancer (LAPC) while stereotactic body radiotherapy (SBRT) is an emerging treatment in this setting. The aim of this study was to compare two cohorts of LAPC patients treated with SBRT +/- CHT versus CRT +/- CHT in terms of local control (LC), distant metastases-free survival (DMFS), progression-free survival (PFS), overall survival (OS), and toxicity.

Materials and Methods: Eighty patients were included. Patients in the two cohorts were matched according to: age ≤/> 65 years, tumor diameter (two cut-offs: </≥ 3.0 and </≥ 3.9 cm), clinical tumor stage and clinical nodal stage, neoadjuvant CHT, and adjuvant CHT. Median prescribed total dose was 30.0 Gy (range: 18.0-37.5) and 54.0 Gy (18.0-63.0) in SBRT and CRT cohorts, respectively. Toxicity was evaluated by CTCAE v4.0 scale. Survival curves were calculated by Kaplan-Meier method. For hypothesis testing an equivalence and a non-inferiority test was calculated. No statistically significant differences in terms of acute and late toxicity, DMFS, PFS, and OS were recorded among the two cohorts.

Results: Median, 1-, and 2-year LC was: 16.0 months, 53.1%, and 40.5% in the CRT cohort and 22.0 months, 80.4%, and 49.8% in the SBRT cohort, respectively (p: 0.017). A statistically non-inferiority significance was recorded in terms of OS between CRT and SBRT (p= 0.031).

Conclusions: Patients treated with SBRT showed higher LC rate and similar OS compared to CRT. Therefore, the design of confirmatory randomized studies comparing SBRT and CRT seems justified.

INTRODUCTION

Pancreatic adenocarcinoma (PC) is a dismal disease with 8% 5-year overall survival (OS) rate (1). It represents the fourth leading cause of mortality in the USA. Epidemiological studies predict that in 2030 PC will rise to second place in the same country (2). Moreover, only 20% of highly selected patients have a potentially resectable disease whereas 30-40% of patients present at diagnosis with non-metastatic unresectable locally advanced PC (LAPC) (3).

Chemotherapy (CHT) and/or chemoradiation (CRT) are considered as treatment options for LAPC (4) despite conflicting results from the randomized trials that compared these two strategies (5-7). Particularly, median OS of LAPC patients treated with CRT plus CHT ranges from 9 to 16 months in the randomized trials published since 2000 (5,6,8,9).

Stereotactic body radiotherapy (SBRT) is an emerging radiotherapy technique, that was pioneered in the LAPC setting by the Stanford group since 2004 (10). The highly conformed dose distribution achievable with SBRT allows the delivery of high biologically effective doses (BED) with the potential to overcome the PC radio-resistance and therefore improving local control (LC) (11-13). Moreover, considering the short duration, SBRT favors the sequential combination with CHT. In fact, SBRT can be completed in a few days unlike standard CRT whose duration is generally between 4-5 weeks. Based on these potential advantages, studies comparing SBRT and CRT seem to be justified. However, only few retrospective analyses are currently available (14-17).

Therefore, we performed a matched case-control study comparing two cohorts of LAPC patients treated with SBRT +/- CHT or CRT +/- CHT in terms of LC, progression-free survival (PFS), distant metastases-free survival (DMFS), and OS. The aim of this report is to present the results of this analysis.

MATERIALS AND METHODS

Study design

This is a multicentric, retrospective, case-control study. On behalf of the AIRO (Italian Association of Radiation Oncology and Clinical Oncology) Gastrointestinal Study Group, we collected clinical data on 419 patients from 15 Italian centers. In our database, LAPC patients could have been treated with every possible combination and schedules of CHT and radiotherapy delivered with any technique.

For the purpose of this analysis, we selected all LAPC patients (56) treated with SBRT from 6 different Italian centers. Secondly, we matched these 56 SBRT patients with the ones treated with CRT (298) according to the following criteria: age ≤/> 65 years, tumor diameter (</≥ 3cm, and </≥ 3.9 cm), clinical tumor stage (cT), clinical nodal stage (cN), administration of neoadjuvant and adjuvant CHT. Matching was performed, blinded to patient outcome, in a 1:1 ratio and when multiple patients matched, one was selected at random. At the end of this selection, we obtained two cohorts of 40 patients each, treated with SBRT or CRT, respectively.

Endpoints

The purpose of this analysis was to compare SBRT +/- CHT and CRT +/- CHT in LAPC patients in terms of different outcomes: LC, DMFS, PFS, and OS. Our aim was also to test the non-inferiority of SBRT compared to CRT.

Eligibility

LAPC patients without metastatic disease and not previously treated with surgery due to PC or with abdominal radiotherapy were included in this study.

Treatment

Details about SBRT treatment were previously described.[18] CRT patients were planned and treated in supine position using a customized foam cradle. CT-simulation was performed with intravenous and oral contrast. CRT was delivered using three-dimensional conformal radiotherapy (70.0%), intensity modulated radiotherapy (IMRT) (20.0%), or volumetric

modulated arc therapy (VMAT) (10.0%). The clinical target volume (CTV) was defined as the gross tumor volume plus a 1-2 cm margin in the pancreatic parenchyma. Regional nodes were included in the CTV based on the tumor site. The planning target volume was defined as the CTV plus an anisotropic margin of 0.5-1 cm radially and 1-2 cm in cranial-caudal direction in most patients. In 57% of patients, the planning target volume was defined using a 4D-CT-simulation. Dose specification and prescription were based on ICRU (International Commission on Radiation Units & Measurements) report 62 and 83 for three-dimensional conformal radiotherapy and IMRT/VMAT, respectively. All patients were treated with conventionally fractionated radiotherapy (1.8-2 Gy/fraction) plus concurrent CHT.

Follow-up

The first follow-up visit was carried out three weeks after the end of radiotherapy. Further evaluations were planned with 3 months intervals. Patients were monitored with standard blood tests, medical history, physical examination, and contrast enhanced CT scans of chest and abdomen.

Statistical analysis

Descriptive statistics included median and percentages for continuous and categorical variables, respectively. Categorical variables were compared using the Pearson's Chi-square test. For hypothesis testing an equivalence and a non-inferiority test was calculated. Survival curves were calculated using the Kaplan Meier method[19] and compared using the log-rank test.[20] A multivariable Cox model[21] was built to test if some clinical and pathological factors could influence outcomes. All tests were two-sided and a p value < 0.05 was considered significant. All endpoints were calculated from the date of radiotherapy start. Statistical analysis was performed with IBM SPSS Version 22.0 (IBM Corp, Armonk, NY, USA) and Statgraphics software systems (full system 5.25 version 4.0- Graphics system by Statistical Graphics Corporation Ed. United States. 1989). Toxicity was scored using the CTCAE v. 4.0 scale.

Ethical issues

All enrolled patients signed a written informed consent. The study (PAULA-1: Pooled Analysis in Unresectable Locally Advanced pancreatic cancer) was approved by our institutional review board (201/2015/O/OssN).

RESULTS

The characteristics of patients and treatment in the two cohorts are shown in **Table I**. Median follow-up was 15 months (range: 3-70). Median total dose, median dose per fraction, and median total $BED_{\alpha/\beta 10Gy}$, were 30.0 Gy (range: 18.0-37.5), 6.0 Gy (range: 5.0-10.0), and 48.0 Gy (range: 28.8-65.6) in the SBRT cohort while the corresponding values were 50.4 Gy (range: 18.0-63.0), 1.8 Gy (range: 1.8-2.1), and 59.4 Gy (range: 21.2-76.2) in the CRT cohort.

The prescribed concurrent CHT regimens were gemcitabine- (80.0%) or capecitabine-based (20.0%). In both cohorts, 60.0% and 22.5% patients underwent neoadjuvant and adjuvant CHT, respectively. Details on the CHT regimens used before and after radiotherapy in the two cohorts are shown in **Table I**.

There were no statistically significant differences neither in terms of acute (p=0.175) nor late gastrointestinal toxicity (p=0.244) comparing LAPC patients treated with SBRT or CRT, respectively. Only one case (2.5%) of gastrointestinal bleeding was recorded 9 months after SBRT.

At univariate analysis, there were no differences between SBRT and CRT treatment in terms of OS (p=0.470), PFS (p=0.749) and DMFS (p=0.610) (**Table II**). Patients treated with SBRT had a statistically significant LC improvement (**Figure 1**) compared to those treated with CRT (median LC: 22 months vs. 16 months, respectively; p=0.017).

Figure 2 and **3** represent the multivariate sub-group analyses of the effects of patients' demographics, disease characteristics, and treatment details of both treatment impact on OS and LC. SBRT was associated with improved LC in the subsets of patients with tumor diameter ≤ 3.9

cm, tumor diameter ≥ 3.0 cm, cT4 and cN0 stage, while in no subset was there any advantage in terms of OS from the two therapeutic modalities.

Finally, a statistically significant non-inferiority in terms of OS was demonstrated between patients treated with SBRT and CRT (p=0.031).

DISCUSSION

At the best of our knowledge, this is the first matched case-control study in LAPC patients comparing conventionally fractionated CRT and SBRT in terms of different clinical outcomes. No differences in terms of OS, PFS, and DMFS were recorded while an improved LC in the SBRT cohort was registered.

Previously, some non-matched studies (16, 22) directly compared these two treatments reporting no significant differences in terms of outcomes. However, de Geus and colleagues (15) and Zhong and colleagues (17) compared matched cohorts treated with SBRT and CRT reporting improved median OS in the SBRT patients' group (**Table II**). In fact, de Geus and colleagues (15), in a registry study from the National Cancer Data Base on LAPC, reported higher median OS after SBRT plus CHT compared to CHT alone (p<0.001), to standard radiotherapy plus CHT (p=0.018), and to IMRT plus CHT (p=0.049). In another analysis also from the National Cancer Data Base (17), a higher 2-year OS rate was recorded in the SBRT +/- CHT cohort, compared to conventionally fractionated radiotherapy +/- CHT (p<0.001) (**Table II**). Similarly, in the meta-analysis of Tchelebi and colleagues (23), including nine studies on SBRT and 11 studies on CRT in LAPC (1147 patients), an improved 2-year OS in SBRT patients was reported (26.9% vs. 13.7%, respectively; p=0.004).

Unlike the studies mentioned above, (15, 17, 23) our study did not show significant differences between SBRT and CRT in terms of OS. This difference could be due to the relatively small sample size of our series and to the relatively low $BED_{\alpha/\beta 10Gy}$ delivered in our SBRT cohort. In fact, median $BED_{\alpha/\beta 10Gy}$ was significantly lower in the latter compared to the

CRT cohort (48.0 Gy vs. 59.4 Gy, respectively; $p<0.001$). The significant correlation recently reported by our group among $BED_{\alpha/\beta 10Gy} \geq 48$ Gy and improved OS in SBRT of LAPC (18) seems to confirm that the lack of improved OS in our SBRT cohort could depend on the relatively low $BED_{\alpha/\beta 10Gy}$.

As mentioned above, the most interesting result of our analysis is the higher LC rate in patients undergoing SBRT compared to CRT, despite the lower median $BED_{\alpha/\beta 10Gy}$ in the SBRT cohort. This difference could be explained by the extremely shorter duration of SBRT compared to CRT which could prevent tumor repopulation during therapy. Similarly, in their retrospective unmatched study, Lin and colleagues (14) reported significantly improved LC for LAPC patients treated with SBRT plus CHT compared to IMRT plus CHT. On the contrary, in their unmatched comparison, Park and colleagues (16) did not observe significant differences in terms of LC between SBRT +/- induction CHT and IMRT +/- induction CHT. These conflicting results (**Table II**) justify the design of randomized studies which may clarify this topic.

More generally, the results recorded in our two cohorts are similar to the ones reported in other studies on SBRT or CRT in LAPC. In fact, 1-year LC was 80.4% in our SBRT cohort, which is consistent with the pooled 1-year LC (72.3%) reported in the systematic review of Petrelli and colleagues (24) on 1009 patients treated with SBRT in LAPC. Similarly, the median LC was 16 months in our CRT cohort, hence consistent with the median LC reported in the two arms of the SCALOP trial on conventionally fractionated CRT in LAPC (12.0 and 14.6 months) (9). Similar analogies can be observed in terms of OS. Our result in terms of median OS in the SBRT cohort (16 months) is similar to that of the two systematic reviews of Petrelli and colleagues (24) (17 months) and Brunner and colleagues (25) (11 months). Moreover, our results in terms of median OS (21.0 months) in the CRT cohort were at least not inferior to those reported in the SCALOP (9) and LAP07 (6) randomized trials (13.4-15.2 months).

Beyond the case-control design of our analysis, the relative analogy between the results recorded by us with those reported in literature makes the findings of our comparison further reliable.

Our analysis showed no significant differences in terms of both acute and late toxicity between SBRT and CRT. This result contrasts with those reported in other studies. Indeed, Park and colleagues (16) recorded significantly lower acute gastrointestinal toxicity grade ≥2 rates using SBRT compared to IMRT (p=0.008). Moreover, the metanalysis of Tchelebi and colleagues (23) showed a significantly higher grade 3-4 acute toxicity in patients treated with standard radiotherapy compared to SBRT, while no differences between the two treatments were recorded in terms of late toxicity. The lack of difference in terms of toxicity observed in our series may be due to several factors such as the small sample size and the retrospective study design. In fact, the latter could have led to an incomplete recording of adverse events. Moreover, the impact of the small sample size on the failure to detect differences in toxicity seems confirmed by the enrolment of only 40 patients in a study reporting similar adverse event rates between SBRT and IMRT (**Table II**) (14). Obviously, also this topic deserves further investigations.

As in any retrospective analysis our study has intrinsic limitations. Even if we used several matching criteria, the assignment to SBRT or CRT was not randomized. Therefore, we cannot rule out that our analysis is affected by bias. Particularly, although the percentage of patients undergoing neoadjuvant and adjuvant CHT was the same in the two cohorts, the used regimens were different among them. Furthermore, the relatively small sample size may have limited the possibility to detect significant differences, particularly in the subset analyses.

CONCLUSIONS

In conclusion, our comparison between SBRT and CRT suggests the equivalence in terms of most outcomes among the two techniques. Furthermore, for the first time using a case-

control methodology, an advantage of SBRT in terms of LC was recorded. This result, together with the logistical advantage of SBRT shorter duration, makes this technique an acceptable option in the treatment of LAPC in combination with CHT. Prospective trials are needed to better compare these two treatments. Moreover, considering that in most cases LAPC treatment has a palliative purpose, these studies should include an accurate assessment of quality of life and symptoms control, especially in terms of pain relief. In fact, both conventional radiotherapy (26) and SBRT (27) are able to improve this symptom but direct comparisons of their relative effectiveness are lacking. Finally, considering that the only possibility of cure for patients with LAPC is to achieve a tumor downstaging to allow a radical surgical resection, the rate of resectability after SBRT and CRT should represent another relevant end point.

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TABLES

Table I: Comparison between the two cohorts of patients treated with chemoradiation and SBRT.

Variable	Value	CRT	SBRT	p
Age (years)	Median (range)	67 (36-89)	67 (36-83)	
	≤ 65	17 (42.5)	17 (42.5)	0.589
	> 65	23 (57.5)	23 (57.5)	
Gender	Male	24 (60.0)	27 (67.5)	0.321
	Female	16 (40.0)	13(32.5)	
ECOG PS	0	22 (55.0)	20 (50.0)	0.493
	1	16 (40.0)	15 (37.5)	
	2	2 (5.0)	5 (12.5)	
Tumor site	Head	28 (70.0)	24 (60.0)	0.638
	Body	10 (25.0)	13 (32.5)	
	Tail	2 (5.0)	3 (7.5)	
Tumor diameter (cm)	Median (range)	4.0 (1.2-8.7)	4.0 (2.0-7.0)	
	< 3.0	5 (12.5)	5 (12.5)	0.631
	≥ 3.0 and< 3.9	18 (32.5)	18 (32.5)	
	≥ 3.9	22 (55.0)	22 (55.0)	
cT stage	3	11 (27.5)	11 (27.5)	0.599
	4	29 (72.5)	29 (72.5)	
cN stage	0	22 (55.0)	22 (55.0)	0.589
	1	18 (45.0)	18 (45.0)	
Biliary stent	No	15 (37.5)	19 (47.5)	0.078
	Yes	23 (57.5)	13 (32.5)	
	Unknown	2 (5.0)	8 (20.0)	
Neoadjuvant chemotherapy	No	16 (40.0)	16 (40.0)	0.590
	Yes	24 (60.0)	24 (60.0)	
Neoadjuvant chemotherapy regimen	Gemcitabine	8 (33.3)	3 (12.5)	0.002*
	Folfox	1 (4.2)	1 (4.2)	
	Folfirinox	2 (8.3)	6 (25.0)	
	Gemcitabine + Nab-placlitaxel	0 (0.0)	9 (37.5)	
	Gemcitabine + Oxaliplatinum	13 (54.2)	5 (20.8)	
Adjuvant chemotherapy	No	31 (77.5)	31 (77.5)	0.605
	Yes	9 (22.5)	9 (22.5)	
Adjuvant chemotherapy regimen	Gemcitabine	7 (77.8)	2 (22.2)	0.073
	5-Fluorouracil	0 (0.0)	1 (11.1)	
	Folfirinox	1 (11.1)	4 (44.4)	
	Gemcitabine + Nab-placlitaxel	0 (0.0)	2 (22.2)	
	Gemcitabine + Oxaliplatinum	1 (11.1)	0 (0.0)	
Acute gastrointestinal toxicity	0	24 (60.0)	31 (77.5)	0.175
	1	12 (30.0)	8 (20.0)	
	2	4 (10.0)	1 (2.5)	
Late gastrointestinal toxicity	0	35 (92.1)	39 (97.5)	0.244
	1	1 (2.6)	0 (0.0)	
	2	2 (5.3)	0 (0.0)	
	3	0 (0.0)	1 (2.5)	

Legend: ECOG PS: *Eastern Cooperative Oncology Group* Performance Status; *: significant p value.

Table II: Characteristics and main findings of studies comparing SBRT +/- CHT versus CRT +/- CHT in locally advanced pancreatic cancer

Author, year	Study design	patients	No patients of the compared treatment	Main findings
Lin J, 2015 [14]	Retrospective	41	20 SBRT +/- cCHT vs 21 IMRT +/- cCHT	Median, 1-y OS: 20.0 vs 13.0 months, 80.0% vs 70.7% (p= 0.127) Median, 1-y LC: 17.5 vs 10.0 months, 70% vs 37.0% (p= 0.004)
Park JJ, 2017 [16]	Retrospective Unmatched cohort	270	44 SBRT +/- iCHT vs 226 IMRT +/- iCHT +/- cCHT	1- and 2-y OS: 56.2%, 25.7% vs 59.6%, 27.2% (p= 0.75) 1- and 2-y LF: 34.4%, 48.7% vs 30.2%, 45.5% (p= 0.51) 1-y DF: 61.7% vs 52.4% (p= 0.25) 1-y DF + LF: 71.5% vs 63.5% (p= 0.18) G2-G3 GI acute toxicity: 7% vs 24% (p= 0.008); 0% vs 2% (p= 1.00) Resection rate: 7% vs 17% (p= 0.11)
de Geus SWL, 2017 [15]	Registry study (NCDB) Unmatched cohort	14331	5464 CHT vs 6418 CRT vs 322 SBRT + CHT vs 2127 IMRT + cCHT	Median OS: 9.9 vs 10.9 vs 13.9 vs 12.0 months, (p< 0.001)
	Matched cohort†	644	322 SBRT + CHT vs 322 CHT 322 SBRT + multiagent CHT vs 322 multiagent CHT 322 SBRT + CHT vs 322 CRT 322 SBRT + CHT vs 322 IMRT + cCHT	Median OS: 13.9 vs 10.2 months, (p< 0.001) Median OS: 14.8 vs 12.9 months (p= 0.095) Median OS: 13.9 vs 11.6 months, (p= 0.018) Median OS: 13.9 vs 12.2 months, (p= 0.049)
Zhong J, 2017 [17]	Registry study (NCDB) Unmatched cohort	8450	631 SBRT vs 7819 CRT	Resection rate: 10.8% vs 9.2% (p= 0.410) Negative resection margin: 92% vs 84% (p= 0.062) 2-y OS: 20.3% vs 16.3% (p< 0.001)
	Matched cohort‡	988	494 SBRT vs 494 CRT	Median OS: 13.9 vs 11.6 months, (p< 0.001) 2-y OS: 21.7% vs 16.5% (p= 0.001)
Chapman BC, 2018 [22]	Retrospective Unmatched cohort	29	22 SBRT + iCHT vs 7 IMRT + iCHT	Median PFS: 8.6 vs 12.5 months (p= 0.349) Median OS: 19.7 vs 21.1 months (p= 0.966)
Present study	Retrospective Matched cohort§	80	40 SBRT +/- CHT vs 40 CRT +/- CHT	Median, 1-y, and 2-y OS: 16.0 vs 21.0 months, 79.8% vs 73.8%, 14.7% vs 40.1% (p= 0.470) Median, 1-y, and 2-y LC: 22.0 vs 16.0 months, 80.4% vs 53.1%, 49.8% vs 40.5% (p= 0.017) Median, 1-y and DMFS: 16.0 vs 12.0 months, 64.5% vs 49.3%, 20.3% vs 41.7% (p= 0.610) Median, 1-y, and 2-y PFS: 14.0 vs 12.0 months, 59.1% vs 49.2, 59.1% vs 32.4% (p= 0.749) GI acute toxicity: G1: 20.0% vs 30.0%; G2: 2.5% vs 10.0% (p= 0.175) GI late toxicity: G1: 0.0% vs 2.6%; G2: 0.0% vs 5.3%; G3 2.5% vs 0.0% (p= 0.244)

Legend: cCHT: concomitant chemotherapy; CHT: chemotherapy; CRT: chemoradiotherapy; DF: distant failure; DMFS: distant metastases-free survival; GI: gastrointestinal; G: grade; iCHT: induction chemotherapy; IMRT: intensity-modulated radiation therapy; LC: local control; LF: local failure; NCDB: National Cancer Database; OS: overall survival; PFS: progression-free survival; SBRT: stereotactic body radiotherapy; †by: age, sex, race, comorbidity, insurance, type of treatment center, tumor location (head or body), clinical stage; ‡by: age, Charlson score, AJCC clinical T and N staging, median tumor size, CT use, year of diagnosis, receipt of surgery; § by: age, AJCC clinical T and N staging, tumor diameter, neoadjuvant CT use, adjuvant CT use.

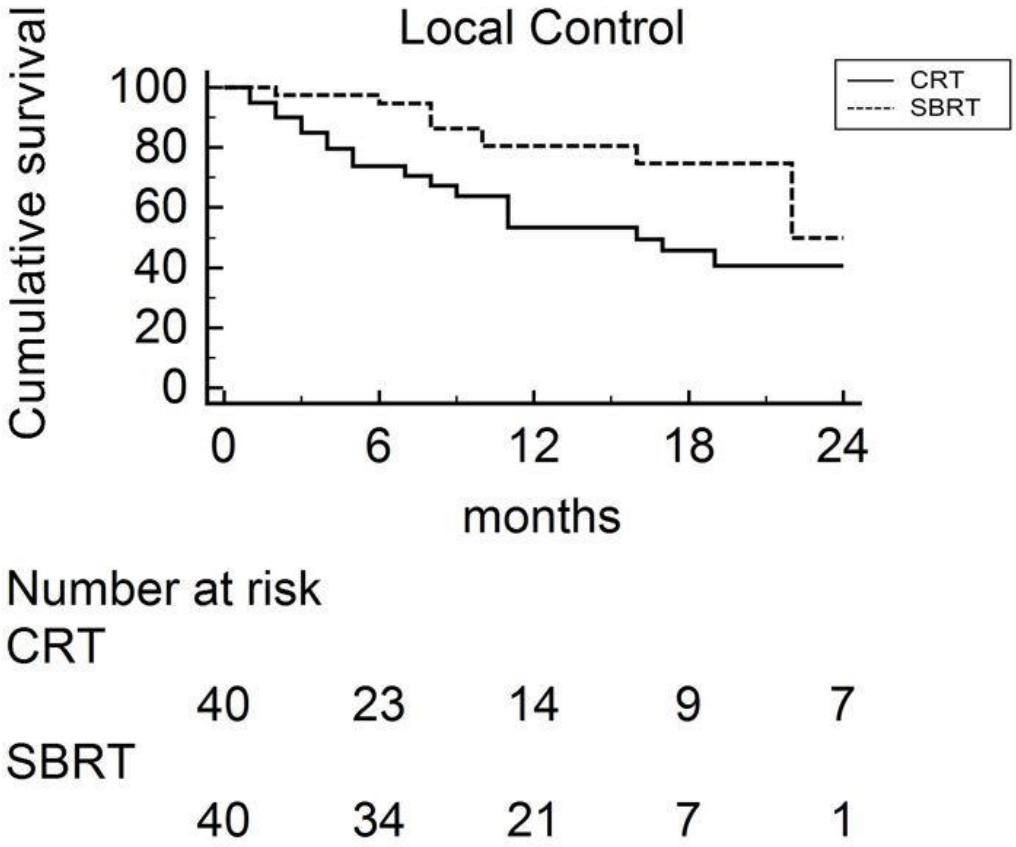
FIGURE LEGENDS

Figure 1: Local control of the two cohorts of patients treated with external beam chemoradiation (CRT) versus stereotactic body radiotherapy (SBRT).

Figure 2: Multivariate subgroup analyses of the effects of patient characteristics on overall survival, comparing patients treated with external beam chemoradiation (CRT) versus stereotactic body radiotherapy (SBRT).

Figure 3: Multivariate subgroup analyses of the effects of patient characteristics on local control, comparing patients treated with external beam chemoradiation (CRT) versus stereotactic body radiotherapy (SBRT).

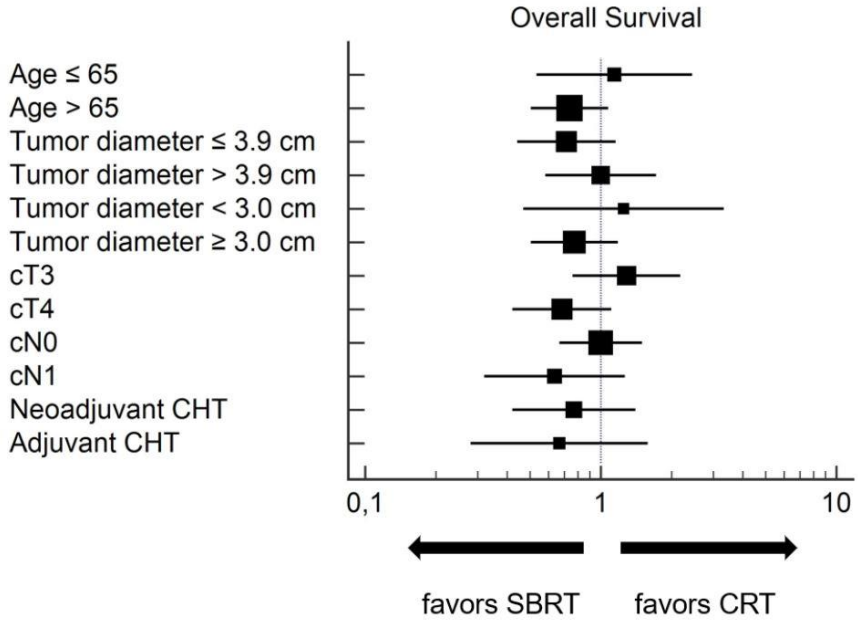
Figure 1



Number at risk

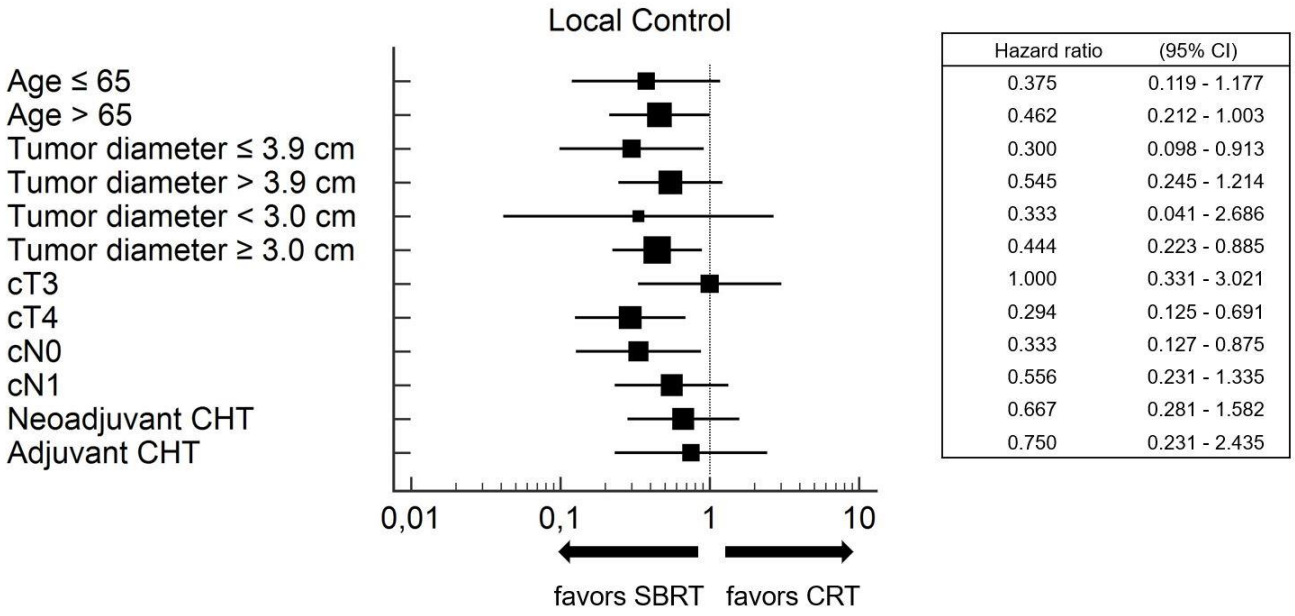
CRT	40	23	14	9	7
SBRT	40	34	21	7	1

Figure 2



Hazard Ratio	(95% CI)
1.143	0.535 - 2.443
0.737	0.505 - 1.075
0.714	0.441 - 1.156
1.000	0.583 - 1.715
1.250	0.469 - 3.331
0.773	0.505 - 1.183
1.286	0.759 - 2.177
0.684	0.422 - 1.108
1.000	0.668 - 1.497
0.636	0.320 - 1.264
0.769	0.422 - 1.401
0.667	0.281 - 1.582

Figure 3



Hazard ratio	(95% CI)
0.375	0.119 - 1.177
0.462	0.212 - 1.003
0.300	0.098 - 0.913
0.545	0.245 - 1.214
0.333	0.041 - 2.686
0.444	0.223 - 0.885
1.000	0.331 - 3.021
0.294	0.125 - 0.691
0.333	0.127 - 0.875
0.556	0.231 - 1.335
0.667	0.281 - 1.582
0.750	0.231 - 2.435

PAULA-3 Outcome analysis of different therapeutic option in locally advanced pancreatic cancer: a predictive model from a multicenter study

ABSTRACT

Aim: Guidelines report a wide range of options in locally advanced pancreatic cancer (LAPC): definitive chemotherapy (CHT) or chemoradiotherapy (CRT) or the emerging stereotactic body radiotherapy (SBRT +/- CHT). Purpose of this analysis was to retrospectively compare these three different therapeutic approaches (CHT, CRT, and SBRT +/- CHT) in terms of different outcomes: overall survival (OS), local control (LC), distant metastasis free-survival (DMFS) and also to propose a predictive model for LC in LAPC.

Materials and Methods: LAPC cases from a multicentric retrospective database (PAULA-1) treated with definitive CHT, or CRT, or SBRT+/- CHT were included. Kaplan-Meier survival curves were tested with the log-rank test. Multivariate Cox proportional hazards were calculated to look for predictors of LC, OS and DMFS. A predictive model for LC in LAPC was developed based on random forest machine learning method.

Results: Median follow-up was 16.6 months (range: 3.0-92.0). Of the 419 LAPC included, 298 (71.1%) were treated with CRT, 65 (15.5%) with CHT and 56 (13.4%) with SBRT. At univariate and multivariate analysis, tumor of the pancreatic body (p=0.002) and SBRT+/- CHT treatment were both factors significantly related to improved LC. At univariate analysis and multivariate analysis, both tumor location at the tail (p= 0.043) and ECOG 2 status (p=0.009) were confirmed to be significantly related to improved OS and worse OS, respectively. At multivariable analysis, increases of CA19-9 negatively impacted on OS, LC, DMFS. Finally, the preliminary LC predictive model reached an AUC of 68% (CI 58,7%-77,4%).

Conclusions: Results for SBRT +/CHT are comparable to the standard of care of definitive CHT and CRT, in terms of OS and DMFS. SBRT+/- CHT seems to be a therapeutic option in LAPC significantly improving LC. Furthermore, we have shown the potential of a predictive model for LC. Randomized trials are needed to compare these different therapeutic options in LAPC using larger validation dataset, especially investigating the emerging role of SBRT.

INTRODUCTION

Five-year overall survival (OS) of pancreatic cancer (PC) ranges between 7% to 10% (1). Moreover, PC is estimated to become the second leading cause of mortality related to cancer within 2030 (2).

Locally advanced pancreatic cancer (LAPC) is a category with an intermediate prognosis between resectable and metastatic patients representing 30-40% of newly diagnosed PC (3).

Recent guidelines (4) propose several therapeutic approaches in this setting of LAPC, such as definitive chemotherapy (CHT), combination of CHT and conventionally fractionated radiotherapy (RT), and even CHT combined with advanced RT technique as stereotactic body radiotherapy (SBRT).

This wide range of therapeutic options in LAPC indeed, derive from many conflicting results of phase III randomized trials investigating CHT versus chemoradiotherapy (CRT) (5-7). Conversely, even if randomized phase III trials comparing standard of care with CHT or CRT with SBRT are not available, SBRT is also an emerging chance of cure in PC. In the last ten years some phase II trials (8-11)vhad been conducted to test SBRT combined to CHT in LAPC setting, demonstrating favourable results in terms of OS and local control (LC), maintaining good toxicity profiles. Some evidence, as the systematic review of Tchelebi (12) report a random effect estimates for 2-year OS in LAPC of 26.9% for SBRT versus 13.7% for conventionally fractionated RT (p= 0.004).

According to these evidences, almost three different therapeutic strategies are available for LAPC: CRT, CHT, SBRT +/- CHT. Therefore, randomized trials are needed to compare these different options, especially investigating the emerging role of SBRT.

Based on this background we retrospectively compared these three different therapeutic approaches, CRT, definitive CHT, and SBRT +/- CHT, extracting LAPC patients from a multicentric database (PAULA-1) in terms of different outcomes [OS, LC, distant metastasis free-survival (DMFS)]. Moreover, we proposed a predictive model for LC in LAPC patients.

MATERIALS AND METHODS

Study design

For the purpose of this study, we considered all the 419 patients of a multicentric retrospective database (PAULA-1) in which clinical data were collected on behalf of the AIRO (Italian Association of Radiation Oncology and Clinical Oncology) Gastrointestinal Study Group. PAULA-1 included LAPC cases deriving from 15 institutions in Italy treated either with definitive CHT, or CRT (delivered with conventionally fractionated RT and combined with different CHT schedules and drugs), or SBRT+/- CHT.

Endpoints

The aim of this report was to compare three different therapeutic strategies including SBRT +/- CHT, CRT and definitive CHT in LAPC patients in terms of different outcomes: OS, LC, and DMFS. Our purpose was also to create a predictive model about LC in LAPC.

Eligibility

LAPC patients considered in this study did not undergo upfront surgery or previous abdominal RT and were not metastatic. All the patients enrolled signed written inform consent.

Treatment

Details about SBRT +/- CHT (13) and CRT (14) treatment were previously described, respectively. Patients were treated with definitive CHT or with CRT on a gemcitabine- or fluoropyrimidine-based regimen. SBRT was mostly combined with CHT.

Follow-up

Regular follow-up examinations were carried out firstly three weeks after the treatment, and therefore with intervals of 3 months. Patients were followed-up with blood test, tumor markers, and imaging studies including contrast enhanced CT of chest and abdomen and18-FDG-PET.

Statistical analysis

Descriptive statistics included median and percentages for continuous and categorical variables, respectively. Kaplan-Meier survival curves (15) were tested with the log-rank test (16). Multivariate Cox proportional hazards (17) were calculated to look for independent effects of various parameters. Particularly, Cox regression analyses were carried out to identify predictors of LC, OS and DMFS. A P-value of <0.05 was considered statistically significant. For the development of the machine learning based predictor, we have used random forest model and we have initially imputed missing data using the MissForest algorithm by chaining random forests, this algorithm was defined by Stekhoven, and Buehlmann (18). The features of the model were selected using the variable importance (VIMP) and the minimal depth ranking. The dataset was randomly split into training set (70%) and test set (30%). For the training step, data were used to approximate model parameters then we have used 10-fold cross-validation for training our model in order to decrease risk of model overfitting. Each model's potential to discriminate between LC outcomes was determined using confusion matrix data to compute accuracy, sensitivity, specificity, and the area under the curve (AUC) based on model performance on the test set. Analysis was performed in R using the packages survival [https://CRAN.R-project.org/package=survival], ranger (19) gbm and pROC (20).

Ethical issues

All the patients included signed a written inform consent. The institutional review board of the promoting center obtained the approval (201/2015/O/OssN) of the study protocol.

RESULTS

Patients and treatment characteristics

Patient characteristic are reported in **Table I**. Median follow-up was 16.6 months (range: 3.0-92.0). Two hundred ninety-eight patients were treated with CRT (71.1%), 65 (15.5%) with definitive CHT and 56 (13.4%) with SBRT. Across the three different treatment cohorts (CRT, definitive CHT, and SBRT), the administration of a gemcitabine-based regimen (56.8%) was preferred to a fluoropyrimidine-based regimen (35.3%). Median total dose of 30.0 Gy (range:

18.0-45.0) corresponded to a median total $BED_{\alpha/\beta 10Gy}$ of 48.0 Gy (range: 28.0-78.7) in the SBRT cohort, and median total dose of 50.4 Gy (range: 10.8-66.0) corresponded to a median total BEDα/β10Gy of 59.4 Gy (range: 12.7-115.1) in the CRT cohort, respectively.

Outcomes

Local control

At univariate analysis, both patients with a tumor of the body (p=0.020) and receiving SBRT +/- CHT treatment (p<0.001) showed a statistically significant prolonged LC **(Table II)**. Moreover, multivariable Cox model confirmed these two covariates, tumor location at the body (HR: 0.34, 95% CI 0.17-0.67, p=0.002) and SBRT+/- CHT treatment (HR: 0.47, 95% CI 0.22-0.97, p=0.042) to be both significantly related to improved LC **(Figure 1)**. At multivariable analysis, increases of CA19-9 (p=0.036) and tumor diameter (p=0.031) were both risk factors for local recurrence, respectively.

Multivariable subset analysis conducted only among patients with a tumor of the pancreatic body **(Figure 2)** showed definitive CHT treatment (p=0.038) and CA19-9 (p=0.034) as both statistically significant risk factors related to local recurrence.

Distant metastasis free survival

At univariate analysis, patients with T4 tumors (p<0.001) and patients receiving a $BED_{\alpha/\beta 10Gy} \geq 59.4$ Gy (p=0.039) had a significantly prolonged DMFS. Furthermore, at multivariable model, T4 tumor stage remained a factor independently associated to a prolonged DMFS, while the increase of CA19-9 marker (p<0.001) was statistically related to a lower DMFS **(Figure 3)**.

Overall survival

At univariate analysis, patients with tumors located into the tail had a statistically significant improved OS (p=0.025), while patients with ECOG 2 had a statistically significant worse OS (p=0.007). Besides, at multivariate analysis, both tumor location at the tail (p= 0.043)

and ECOG 2 status (p=0.009) were confirmed to be significantly related to improved OS and worse OS, respectively **(Figure 4)**.

At univariate analysis, patients treated with SBRT +/- CHT showed a statistically significant OS improvement compared to those treated with CRT or CHT alone (median OS: 19 months vs. 15 months vs. 10 months, respectively; $p < 0.001$) **(Table II)**. Conversely, at multivariable model, only a trend toward significance was recorded for definitive CHT as a negative prognostic risk factor for OS (p=0.061).

Moreover, univariate analysis highlighted a trend at limit of statistically significance (p=0.054) in terms of prolonged OS for patients treated with a $BED_{\alpha/\beta 10Gy} \geq 59.4$ Gy.

Furthermore, at Cox model, every unit of incrementation of CA 19-9 was considered a risk factor for OS (p<0.001).

Predictive model

In order to select the features to include in the machine learning based model we have introduced the variable importance (VIMP) and the minimal depth ranking technique (**Supplementary figure S1**). Notably, we have included in the evaluation all the variables with <25% of missing data keeping only one variable in case of high correlation between two or more variables, to avoid multicollinearity. In the final LC model, based on random forest, we have included as features: gender (male/female), age >65 years , age, jaundice (yes/no), treatment category (CRT, CHT, SBRT +/- CHT), tumor diameter (cm), tumor site (head, body, tail), ECOG at diagnosis (0-1-2), clinical tumor stage (cT3-cT4), clinical nodal stage (cN0, cN+), $BED_{\alpha/\beta 10Gy} \geq 59.4$ Gy, biliary stent, CA19-9 (U/mL), pain, reaching an 10 fold cross validation AUC of 68% (**Figure 5**) showing the predictive potential of these variables for LC in LAPC.

DISCUSSION

From a large database of real-life data, we compared the three therapeutic option recommended in current guidelines about LAPC. Definitive CHT and CRT are well-established

options in LAPC (4), while SBRT +/- CHT is an emerging feasible option in this setting. In our study we showed that SBRT +/- CHT was confirmed to be an effective alternative to standard of care (definitive CHT or CRT) in LAPC, indeed improving LC. To our knowledge, we also developed the first predictive model for LC in LAPC.

Some limits characterize our findings. Firstly, the retrospective design might have prevented our results, secondly, some selection bias might be identified, as the sample size is relatively small in contrast to the pathology volume. Notably, LAPC is the most frequent stage at diagnosis for pancreatic cancer. Furthermore, in PAULA-1 database there were some missing data.

However, our predictive model has to be validated in a larger scale, even if it reached an acceptable mean AUC of 68%. Additional data will be essential to validate our results. Besides, our predictive model represents a preliminary model, and it should be used in clinical practice carefully.

At both univariate and multivariate analysis, both patients with a tumor of the body (p=0.002) and receiving SBRT +/- CHT treatment (p=0.042) **(Figure 1)** had an improved LC. Almost 90% of body LAPC of PAULA-1 database were treated with SBRT or CRT. According to their anatomical location, body LAPC are more likely to be effectively treated with SBRT or external beam radiotherapy, because unlike head tumors, they are farer from duodenum, that is easier to spare. These data are partially confirmed by our multivariable subset analysis among body LAPC **(Figure 2)** showing definitive CHT treatment (p=0.038) as a statistically significant risk factor for local recurrence.

In a previous experience from our group (14) SBRT +/- CHT was found to be an effective alternative to CRT in LAPC, in terms of prolonged LC. In this report, we confirm these results, highlighting SBRT+/- CHT as a valid therapeutic option, improving LC (HR: 0.47, 95% CI 0.22-0.97, p=0.042) in a wider cohort of patients. Notably, SBRT delivers ablative doses with

a rapid dose falloff, providing an overcoming of LAPC radio-resistance (21) and allowing optimal sparing of the surrounding gastrointestinal organs (9, 22). Moreover, due to its short duration, SBRT promotes an excellent integration with CHT, minimizing its interruptions (7). Even if progression of disease is mostly related to metastatic disease, some autoptic series on pancreatic cancer (23, 24) reported around 30% mortality due to locally progressive disease. Hence, the challenge in reaching good LC rates in LAPC could be translated in a gain in OS, at least in some patient subsets (25).

Our results in terms of median OS in both the CRT and CHT cohort (15.0 months and 10.0 months, respectively) were comparable to those reported in recent randomized trials SCALOP (26) and LAP07 (6) (15.2 and 16.4 months).

Recent findings from a meta-analysis (12), comparing 1147 LAPC patients receiving SBRT or CRT highlighted an advantage in terms of 2-year OS for SBRT treatment (26.9% vs. 13.7%, respectively; p=0.004). Nevertheless, the advantage in terms of OS for SBRT respect to CRT and CHT recorded at univariate analysis (median OS: 19 months vs. 15 months vs. 10 months, respectively; $p < 0.001$) **(Table II)** was not maintained at multivariable model, reporting only a trend toward significance for definitive CHT as a negative prognostic risk factor for OS (p=0.061). This discrepancy might be statistically due to the paucity of patients receiving SBRT respect to the other two cohort (CRT and CHT).

In our predictive model, according to Minimal depth and VIMP, both the two different ranking methods assumed, agreed in considering variables as treatment category, pain, and $BED_{\alpha/\beta 10Gy}$, predictors of LC (**Supplementary figure S1**). Particularly, treatment category variable including the three treatment options we compared (CRT, CHT, SBRT) was the most important variable influencing LC. Moreover, also a $BED_{\alpha/\beta 10Gy} \geq 59.4$ Gy was a positive predictive factor for LC. Similarly, in another series form our group (13), we found a positive impact of $BED_{\alpha/\beta 10Gy} \geq 48$ Gy delivered with SBRT both on LC and OS.

CONCLUSIONS

We proved that SBRT has a significant impact on LC in LAPC. Moreover, SBRT treatment is comparable to the standard of care (definitive CHT and CRT) in terms of OS and DMFS. Furthermore, we have shown the potential of a predictive model for LC in which the most important predictive variable is treatment. Randomized trials are needed to compare these different therapeutic options in LAPC using larger validation dataset, especially investigating the emerging role of SBRT.

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TABLES

Table I: Patients and treatments characteristics

Variable	Value	Total (%)	CRT (%)	Definitive CT (%)	Stereo (%)
Age (years)	Median (range)	66 (34-90)	67 (34-90)	63 (44-88)	68 (36-89)
	≤ 65	199 (47.5)	140 (47.0)	35 (53.8)	24 (42.9)
	> 65	220 (52.5)	158 (53.0)	30 (46.2)	32 (57.1)
Gender	M	226 (53.9)	164 (55.0)	31 (47.7)	31 (55.4)
	F	193 (46.1)	134 (45.0)	34 (52.3)	25 (44.6)
ECOG	0	167 (39.9)	121 (40.7)	19 (29.2)	27 (48.2)
	1	131 (31.2)	71 (23.8)	37 (56.9)	23 (41.1)
	2	33 (7.9)	21 (7.0)	7 (10.8)	5 (8.9)
	missing	88 (21.0)	85 (28.5)	2 (3.1)	1 (1.8)
Tumor site	Head	283 (67.5)	207 (69.5)	43 (66.2)	33 (58.9)
	Body	105 (25.1)	75 (25.2)	11 (16.9)	19 (33.9)
	Tail	26 (6.2)	12 (4.0)	10 (15.4)	4 (7.2)
	missing	5 (1.2)	4 (1.3)	1 (1.5)	0 (0.0)
Tumor diameter (cm)	Median (range)	3.9 (1.2-10.0)	3.6 (1.4-10.0)	4.0 (2.0-7.0)	3.9 (1.2-8.7)
	<3.0	59 (14.1)	44 (14.8)	8 (12.2)	7 (12.5)
	≥ 3.0 and< 3.9	112 (26.7)	84 (28.2)	9 (13.9)	19 (33.9)
	≥ 3.9	248 (59.2)	170 (57.0)	48 (73.9)	30 (53.6)
cT	3	144 (34.4)	117 (39.3)	10 (15.4)	17 (30.4)
	4	275 (65.6)	181 (60.7)	55 (84.6)	39 (69.6)
cN	0	165 (39.4)	131 (44.0)	0 (0.0)	34 (60.7)
	1	232 (55.4)	156 (52.3)	54 (98.2)	22 (39.3)
	missing	22 (5.2)	11 (3.7)	11 (1.8)	0 (0.0)
Drugs	Gemcitabine-based	238 (56.8)	165 (55.4)	50 (76.9)	23 (41.1)
	Fluopyrimidine-based	148 (35.3)	123 (41.2)	7 (10.8)	18 (32.1)
	Others	18 (4.3)	10 (3.4)	8 (12.3)	
	No	15 (3.6)			15 (26.8)
Total dose (Gy)	Median (range)	50.4 (10.8-66.0)	50.4 (10.8-66.0)		30.0 (18.0-45.0)
BED (α/β 10 Gy)	Median (range)	59.4 (12.7-115.1)	59.4 (12.7-115.1)		48.0 (28.0-78.7)
BED (α/β 10 Gy)	< 59.4 Gy	109 (26.0)	58 (19.5)		51 (91.1)
	≥ 59.4 Gy	245 (58.5)	240 (80.5)		5 (8.9)
	missing	65 (15.5)		65 (100.0)	
Treatment	CRT	298 (71.1)			
	Definitive CT	65 (15.5)			
	Stereo	56 (13.4)			

Table II: Univariate analysis

Variable	Value	1-y OS (%)	2-y OS (%)	Median OS (months)	p	1-y LC (%)	2-y LC (%)	Median LC (months)	p	1-y DMFS (%)	2-y DMFS (%)	Median DMFS (months)	p
Age	≤ 65	61.4	31.0	16	.177	68.3	46.2	21	.124	56.3	37.8	15	.539
	> 65	60.0	22.2	14		60.5	39.3	17		50.9	32.2	13	
Gender	M	61.1	25.9	15	.605	64.3	42.8	18	.629	57.1	39.4	16	.061
	F	60.2	26.6	15		64.0	41.8	20		49.6	30.1	12	
ECOG	0	72.8	39.1	19	.007	63.8	47.7	21	.108	55.1	34.2	14	.824
	1	58.2	23.9	15		52.6	34.2	14		53.7	31.3	14	
	2	56.1	10.9	NR		62.2	0.0	15		48.9	29.3	12	
Tumor site	Head	56.9	21.1	14	.025	61.3	37.5	17	.020	47.8	32.6	12	.289
	Body	65.8	32.6	17		71.1	33.5	28		60.7	35.4	14	
	Tail	76.2	54.3	28		58.8	29.8	17		73.6	43.6	24	
Tumor diameter (cm)	<3.0	64.2	30.5	14	.088	60.0	39.9	15	.191	53.9	26.6	13	.273
	≥ 3.0 and< 3.9	70.1	33.0	16		57.2	33.1	15		48.5	27.8	12	
	≥ 3.9	62.0	22.3	15		68.3	47.3	22		55.8	40.2	15	
cT	3	52.7	19.7	13	.078	63.1	39.9	17	.695	39.0	25.1	10	<.001
	4	65.0	29.9	16		64.7	43.7	20		61.0	40.0	16	
cN	0	68.4	23.9	16	.068	69.4	48.9	21	.081	53.5	40.9	15	.274
	1	55.8	26.6	14		60.7	39.3	17		52.6	33.0	13	
BED (α/β 10 Gy)	< 59.4 Gy	59.9	20.2	15	.054	69.5	56.4	NR	.094	47.6	20.1	12	.039
	≥ 59.4 Gy	68.1	32.6	17		68.5	45.2	20		55.0	41.4	16	
Treatment	CRT	62.2	29.1	15	<.001	66.6	45.4	19	<.001	52.2	34.8	13	.819
	Definitive CT	36.0	12.2	10		42.9	13.8	9		59.1	42.2	15	
	Stereo	81.9	27.1	19		79.0	60.6	NR		55.6	24.0	14	

FIGURE LEGENDS

Figure 1: Multivariate analysis of the effects of patient characteristics and treatments on local control

Figure 2: Multivariate subgroup analysis on tumor of the pancreatic body about the effects of patient characteristics and treatments on local control

Figure 3: Multivariate analysis of the effects of patient characteristics and treatments on distant metastasis free survival

Figure 4: Multivariate analysis of the effects of patient characteristics and treatments on overall survival

Figure 5: Predictive model

Figure S1: Graphical representation of the variable importance (VIMP) and the minimal depth ranking technique

Figure 1:

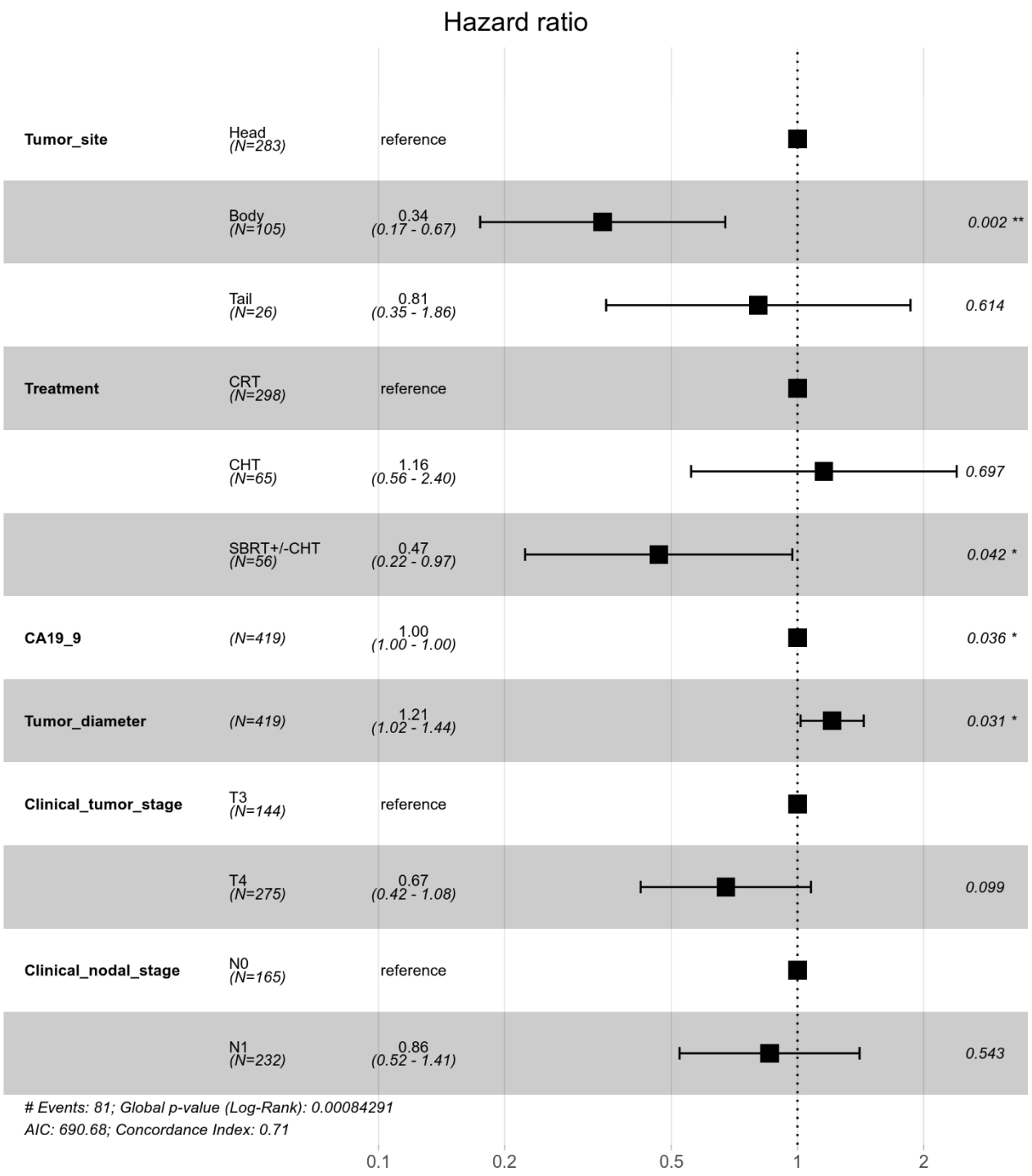

Hazard ratio
Tumor_site
Head (N=283)
reference
Body (N=105)
0.34 (0.17 - 0.67)
0.002 **
Tail (N=26)
0.81 (0.35 - 1.86)
0.614
Treatment
CRT (N=298)
reference
CHT (N=65)
1.16 (0.56 - 2.40)
0.697
SBRT+/-CHT (N=56)
0.47 (0.22 - 0.97)
0.042 *
CA19_9
(N=419)
1.00 (1.00 - 1.00)
0.036 *
Tumor_diameter
(N=419)
1.21 (1.02 - 1.44)
0.031 *
Clinical_tumor_stage
T3 (N=144)
reference
T4 (N=275)
0.67 (0.42 - 1.08)
0.099
Clinical_nodal_stage
N0 (N=165)
reference
N1 (N=232)
0.86 (0.52 - 1.41)
0.543
Events: 81; Global p-value (Log-Rank): 0.00084291
AIC: 690.68; Concordance Index: 0.71
0.1
0.2
0.5
1
2

Figure 2:

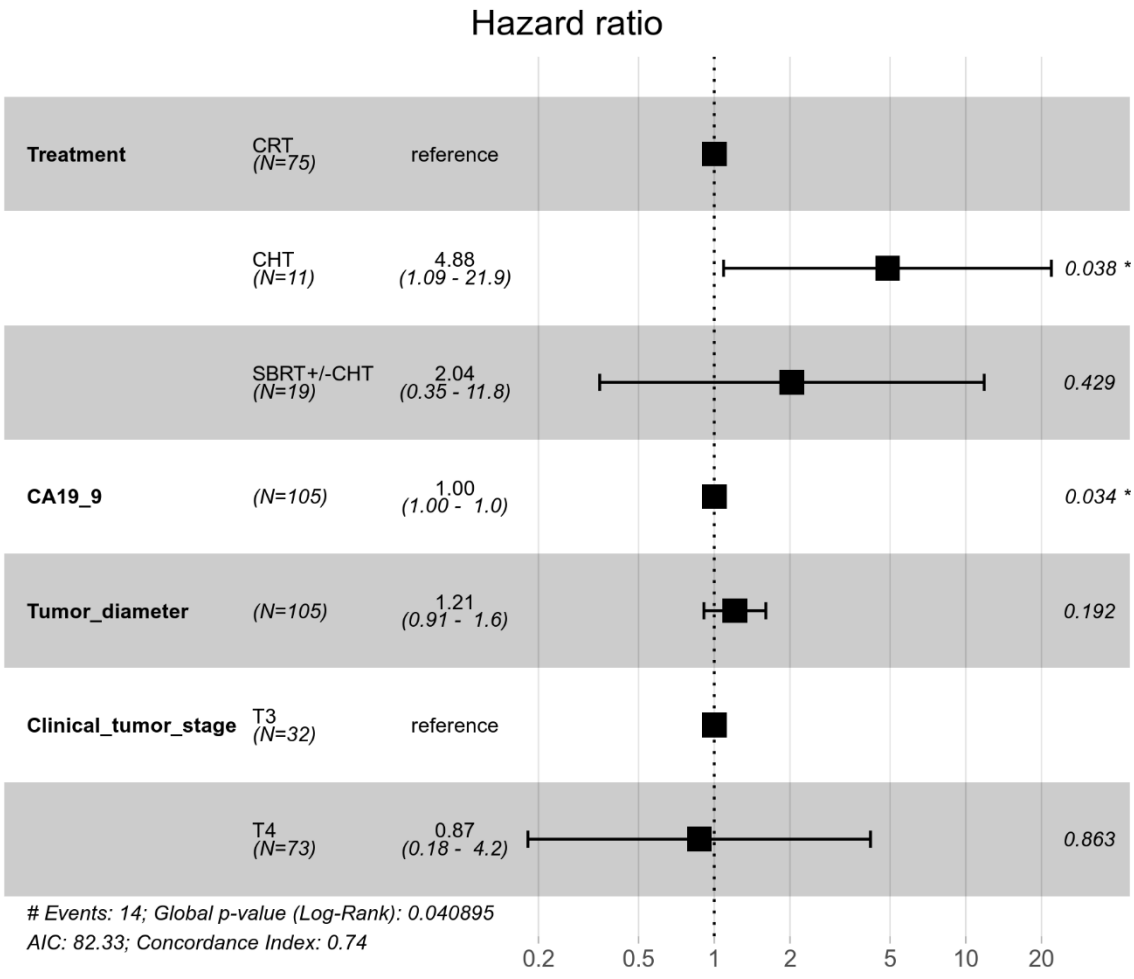

Hazard ratio
Treatment
CRT (N=75)
reference
CHT (N=11)
4.88 (1.09 - 21.9)
0.038 *
SBRT+/-CHT (N=19)
2.04 (0.35 - 11.8)
0.429
CA19_9
(N=105)
1.00 (1.00 - 1.0)
0.034 *
Tumor_diameter
(N=105)
1.21 (0.91 - 1.6)
0.192
Clinical_tumor_stage
T3 (N=32)
reference
T4 (N=73)
0.87 (0.18 - 4.2)
0.863
Events: 14; Global p-value (Log-Rank): 0.040895
AIC: 82.33; Concordance Index: 0.74
0.2
0.5
1
2
5
10
20

Figure 3:

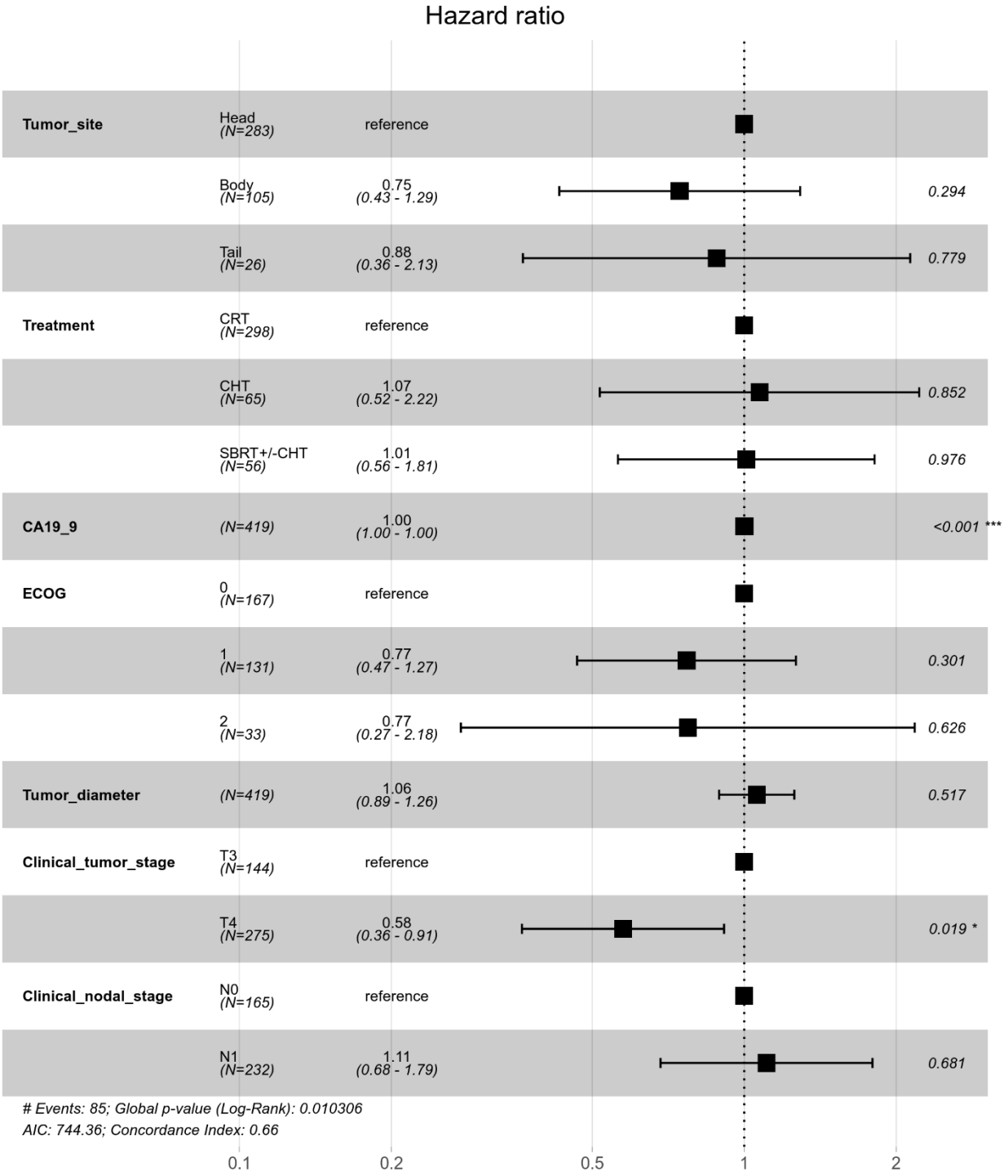

Hazard ratio
Tumor_site
Head (N=283)
reference
Body (N=105)
0.75 (0.43 - 1.29)
0.294
Tail (N=26)
0.88 (0.36 - 2.13)
0.779
Treatment
CRT (N=298)
reference
CHT (N=65)
1.07 (0.52 - 2.22)
0.852
SBRT+/-CHT (N=56)
1.01 (0.56 - 1.81)
0.976
CA19_9
(N=419)
1.00 (1.00 - 1.00)
<0.001 ***
ECOG
0 (N=167)
reference
1 (N=131)
0.77 (0.47 - 1.27)
0.301
2 (N=33)
0.77 (0.27 - 2.18)
0.626
Tumor_diameter
(N=419)
1.06 (0.89 - 1.26)
0.517
Clinical_tumor_stage
T3 (N=144)
reference
T4 (N=275)
0.58 (0.36 - 0.91)
0.019 *
Clinical_nodal_stage
N0 (N=165)
reference
N1 (N=232)
1.11 (0.68 - 1.79)
0.681
Events: 85; Global p-value (Log-Rank): 0.010306
AIC: 744.36; Concordance Index: 0.66
0.1
0.2
0.5
1
2

Figure 4:

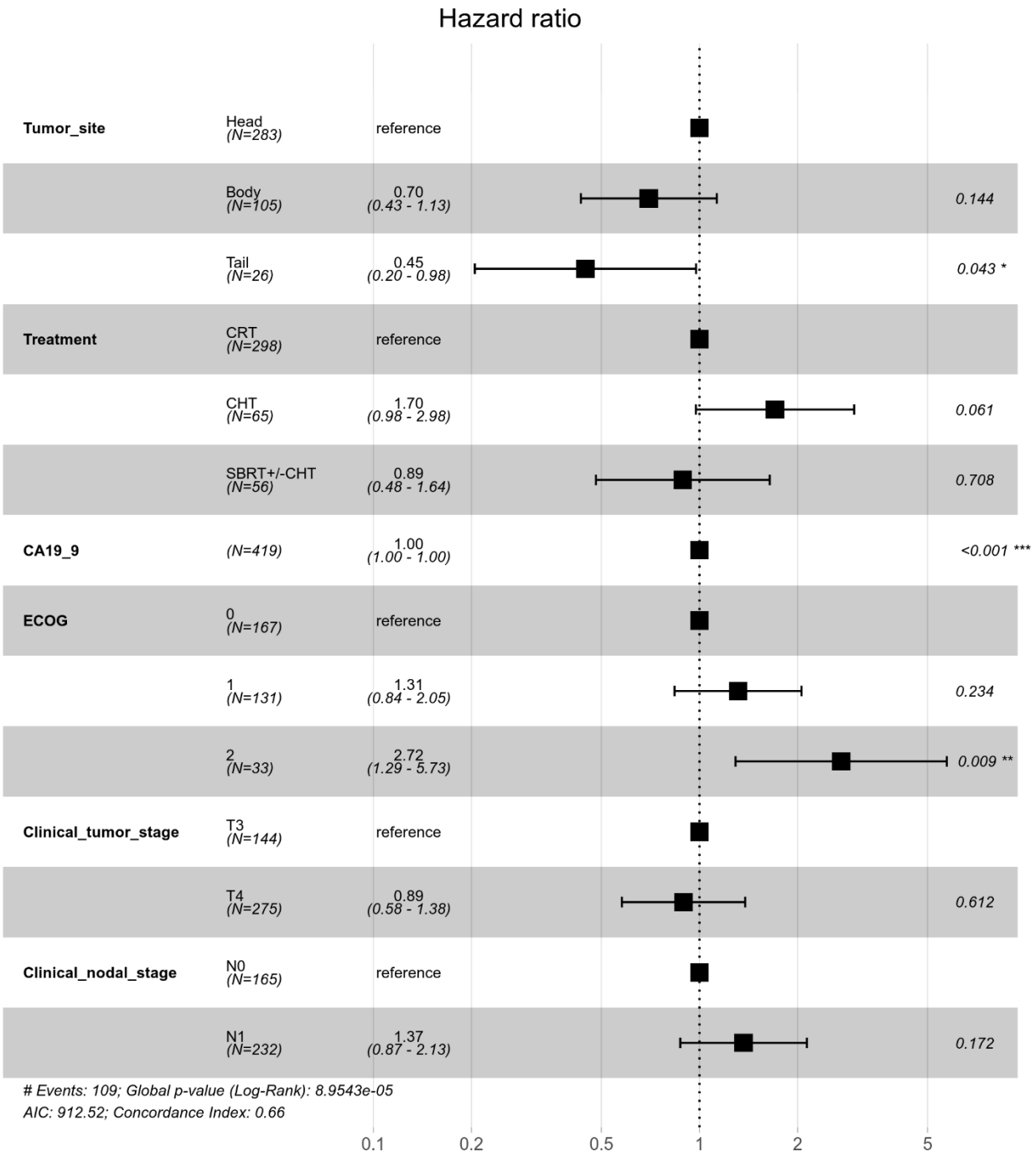
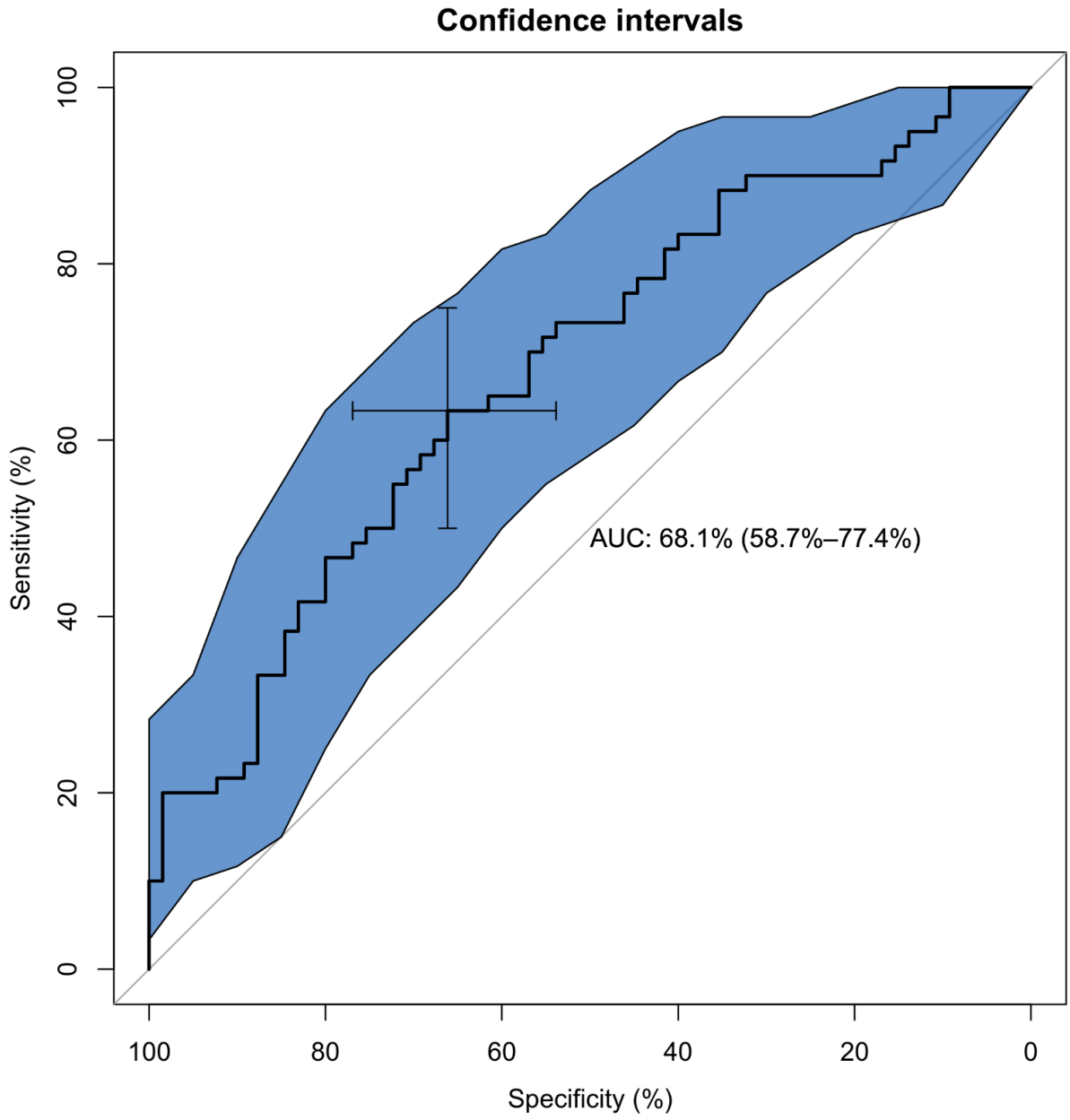
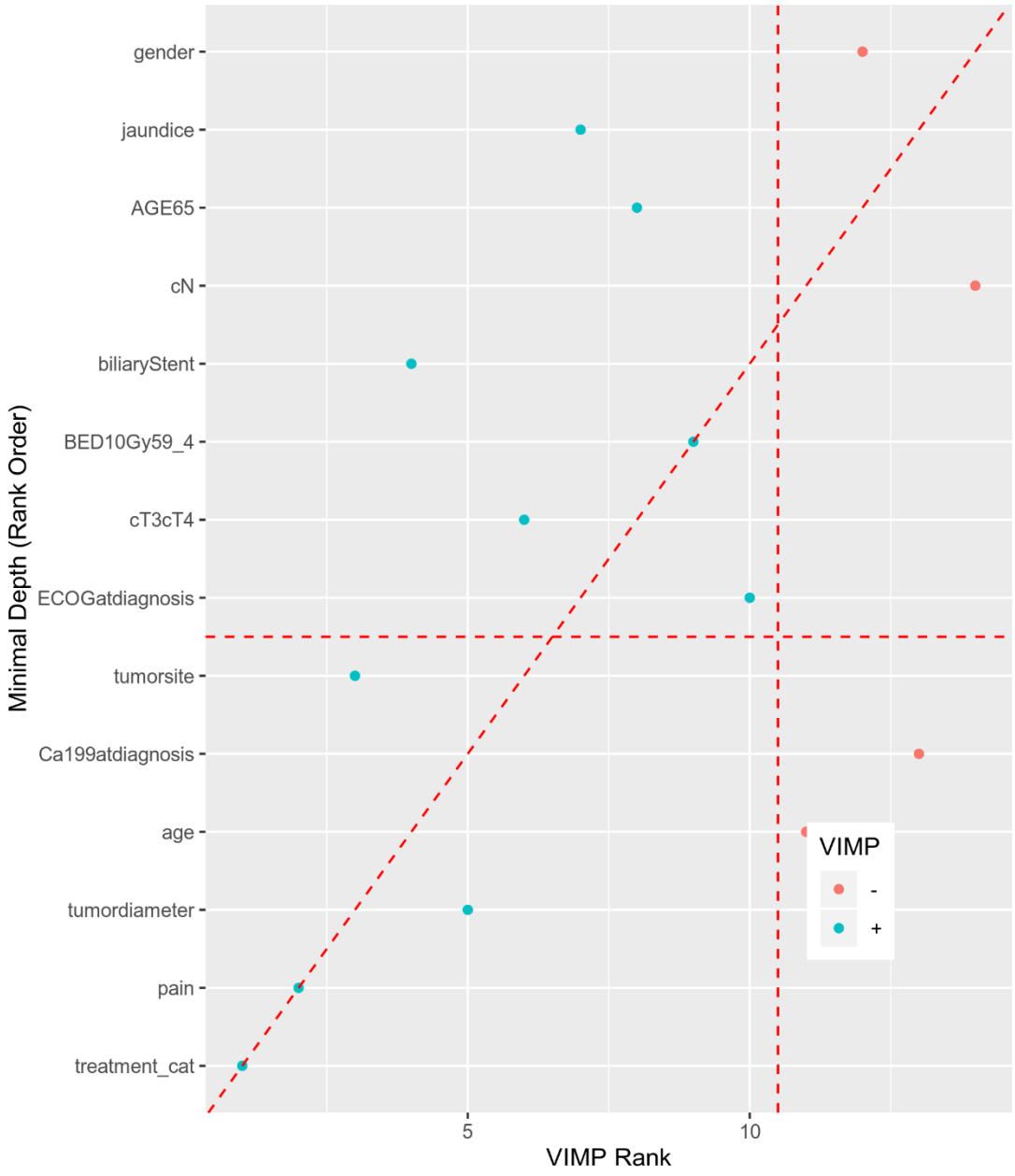

Hazard ratio
Tumor_site
Head (N=283) reference
Body (N=105) 0.70 (0.43 - 1.13) 0.144
Tail (N=26) 0.45 (0.20 - 0.98) 0.043 *
Treatment
CRT (N=298) reference
CHT (N=65) 1.70 (0.98 - 2.98) 0.061
SBRT+/-CHT (N=56) 0.89 (0.48 - 1.64) 0.708
CA19_9
(N=419) 1.00 (1.00 - 1.00) <0.001 ***
ECOG
0 (N=167) reference
1 (N=131) 1.31 (0.84 - 2.05) 0.234
2 (N=33) 2.72 (1.29 - 5.73) 0.009 **
Clinical_tumor_stage
T3 (N=144) reference
T4 (N=275) 0.89 (0.58 - 1.38) 0.612
Clinical_nodal_stage
N0 (N=165) reference
N1 (N=232) 1.37 (0.87 - 2.13) 0.172
Events: 109; Global p-value (Log-Rank): 8.9543e-05
AIC: 912.52; Concordance Index: 0.66
0.1
0.2
0.5
1
2
5

Figure 5:



Measure	Value	Derivations
Sensitivity	0.6333	TPR = TP / (TP + FN)
Specificity	0.6462	SPC = TN / (FP + TN)
Precision	0.6230	PPV = TP / (TP + FP)
Negative Predictive Value	0.6563	NPV = TN / (TN + FN)
False Positive Rate	0.3538	FPR = FP / (FP + TN)
False Discovery Rate	0.3770	FDR = FP / (FP + TP)
False Negative Rate	0.3667	FNR = FN / (FN + TP)
Accuracy	0.6400	ACC = (TP + TN) / (P + N)
F1 Score	0.6281	F1 = 2TP / (2TP + FP + FN)
Matthews Correlation Coefficient	0.2793	TP*TN - FP*FN / sqrt((TP+FP)*(TP+FN)*(TN+FP)*(TN+FN))

Figure S1:


gender
jaundice
AGE65
cN
biliaryStent
BED10Gy59_4
cT3cT4
ECOGatdiagnosis
tumorsite
Ca199atdiagnosis
age
tumordiameter
pain
treatment_cat
Minimal Depth (Rank Order)
5
10
VIMP Rank
VIMP
-
+