


# Isotoxic high-dose stereotactic body radiotherapy integrated in a total multimodal neoadjuvant strategy for the treatment of localized pancreatic ductal adenocarcinoma

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## Abstract

**Background:** Our aim was to evaluate the feasibility and safety of isotoxic high-dose (iHD) stereotactic body radiation therapy (SBRT) in a total neoadjuvant sequence for the treatment of localized pancreatic adenocarcinoma.

**Materials and methods:** Biopsy-proven borderline resectable/locally advanced pancreatic cancer (BR/LAPC) patients were included in this observational prospective analysis from August 2017 to April 2020 without excluding tumours showing a radiological direct gastrointestinal (GI) invasion. An induction chemotherapy by modified fluorouracil, irinotecan and oxaliplatin was performed for a median of six cycles. In case of non-progression, an isotoxic high-dose stereotactic body radiotherapy (iHD-SBRT) was delivered in 5 fractions followed by a surgical exploration. The primary endpoint was acute/late gastrointestinal grade  $\geq 3$  toxicity. Secondary endpoints were overall survival (OS), progression-free survival (PFS) and local control (LC).

**Results:** A total of 39 consecutive patients (21 BR and 18 LAPC) were included: 34 patients (87.2%, 18 BR and 16 LAPC) completed the planned neoadjuvant sequence. After iHD-SBRT, 19 patients [55.9% overall, 13/18 BR (72.2%) and 6/16 LAPC (37.5%)] underwent an oncological resection among the 25 patients surgically explored (73.5%). The median follow up was 18.2 months. The rates of acute and late GI grade 3 toxicity were, respectively, 2.9% and 4.2%. The median OS and PFS from diagnosis were, respectively, 24.5 and 15.6 months. The resected patients had improved median OS and PFS in comparison with the non-resected patients (OS: 32.3 *versus* 18.2 months,  $p=0.02$ ; PFS: 24.1 *versus* 7.1 months,  $p<0.001$ ). There was no survival difference between the BR and LAPC patients. The 1-year LC from SBRT was 74.1% and the median locoregional PFS was not reached for both BR and LAPC patients.

**Conclusions:** iHD-SBRT displays an excellent toxicity profile, also for potentially high-risk patients with radiological direct GI invasion at diagnosis and can be easily integrated in a total neoadjuvant strategy. The oncological outcomes are promising and emphasise the need for further exploration of iHD-SBRT in phase II/III trials.

**Keywords:** neoadjuvant therapy, pancreatic cancer, radiotherapy, stereotactic radiotherapy

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## Introduction

Pancreatic ductal adenocarcinoma (PDAC) is currently the fourth leading cause of cancer-related death with an estimated 5-year overall

survival (OS) rate of 7% for all stages combined.<sup>1,2</sup> Despite the lack of level I evidence, the National Comprehensive Cancer Network (NCCN), the American Societies of Clinical Oncology and

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Radiation Oncology (ASCO, ASTRO) and the American College of Radiobiology (ACR) guidelines have already listed stereotactic body radiotherapy (SBRT) as an optional treatment for localized PDAC in experienced, high-volume centres.<sup>3-7</sup> The SBRT technique presents indeed multiple advantages such as: (a) having an easy incorporation into a total neoadjuvant approach; (b) reduction of long interruptions of full-dose chemotherapy; (c) the potential to improve local control (LC) with the delivery of a higher biologically effective dose (BED); and (d) showing interesting results in PDAC by improving (R0) resections rates and survival.<sup>8</sup> Although the delivery of a higher BED appears to be a predictor of longer survival in several studies, it is usually not easy to achieve in PDAC given the proximity and/or invasion of critical gastrointestinal (GI) organs at risk (OARs), movements of the target during respiration and often consequent tumour diameter.<sup>8-12</sup> A solution to deliver high BED<sub>10</sub> to the tumour without increasing the rates of serious GI toxicity (e.g. stenosis, perforation, ulcer with bleeding...) is the use of an isotoxic dose prescription (IDP). The IDP is based on known OARs tolerance levels to control the tissue complication probability while allowing individual maximization of the dose delivered to the tumour and the tumour-vessel interfaces (TVIs).<sup>13</sup> In an IDP prescription, the dose delivered is individually tailored based on fixed predefined levels of toxicity for the critical OARs according to acceptable normal tissue complication probability. In parallel, the protective planning target volume (PTV) without overlap with the critical OARs is escalated to the technically highest achievable level.<sup>13</sup> The concept of IDP has been recently used in several dose-escalation studies notably for pulmonary radiotherapy (RT) and is particularly well adapted for the delivery of pancreatic high-dose SBRT.<sup>14,15</sup> Based on these data, we wanted to perform a prospective analysis of the safety and feasibility of the integration of isotoxic high-dose (iHD) SBRT into a total neoadjuvant strategy for the treatment of borderline resectable (BR) and locally advanced pancreatic cancer (LAPC). Finally, oncological and surgical outcomes were also evaluated.

## Materials and methods

### Patient selection

This study was approved by the Institutional Review Board of Erasme University Hospital and Institut Jules Bordet under the approval numbers

P2017/168 and CE3285, respectively. Between August 2017 and April 2020, BR or LAPC patients who were deemed to receive the complete neoadjuvant strategy, including modified FOLFIRINOX (mFFX: fluorouracil, irinotecan and oxaliplatin) or gemcitabine plus nab-Paclitaxel (Gem/nP), followed by iHD-SBRT and surgical exploration, were consecutively included in this study. For all patients, written and verbal informed consent, approved by our ethics committee, was provided for all proposed therapeutic strategies. The diagnostic work-up included a triphasic computed tomography (CT) scan of abdomen and thorax, tumour marker (CA19.9), an endoscopic ultrasonography-guided biopsy and optional abdominal magnetic resonance imaging (MRI) and positron emission tomography (PET)-CT according to the local centre facilities. BR and LAPC were defined according to the NCCN criteria<sup>5</sup> and the resectability status was assessed by a centralized multidisciplinary board of pancreatic surgeons and radiologists.

The inclusion criteria were: biopsy-proven BR or LAPC adenocarcinoma; age  $\geq 18$  years; World Health Organization performance status  $\geq 1$ ; no evidence of metastatic disease; largest tumour diameter  $\leq 7$  cm; and normal renal, bone marrow and liver function. Exclusion criteria were prior abdominal RT, pregnant or breastfeeding women, existence of another active neoplasia (a remission period of at least 5 years was mandatory) and initial contraindication of surgery including the presence of a portal cavernoma with collateral vascularization. Tumours presenting a radiological infiltration of the stomach and/or the duodenum were not excluded.

### Chemotherapy

All patients included received an induction with the mFFX chemotherapy regimen. A shift to Gem/nP was authorized in case of intolerance or no response to mFFX after an intermediate restaging at two to four cycles. Patients received their multiagent chemotherapy either at Erasme or Bordet academic institutions or at bespoke facilities, according to the area of residence or patient's preference. A delivery of six cycles of neoadjuvant chemotherapy was encouraged and a minimal number of three cycles was required. mFFX consisted of a 2 h intravenous infusion of oxaliplatin (85 mg/m<sup>2</sup>) followed by a 2 h intravenous infusion of leucovorin (400 mg/m<sup>2</sup>) concomitantly with a 90 min intravenous infusion of irinotecan (180 mg/m<sup>2</sup>), followed by a 46 h continuous infusion of

fluorouracil (2400 mg/m<sup>2</sup>) and was given once every 2 weeks. Dose reduction and delays were according to local practice. In case of oncological resection at the end of the multimodal neoadjuvant strategy, adjuvant chemotherapy was recommended for at least 3 months unless the patient's condition precluded it and the regimen used was left to the choice of the oncologist.

#### *Stereotactic body radiation therapy protocol*

Patients in whom no disease progression was observed on at least thoracic–abdominal CT scan after the completion of the chemotherapy induction were considered for iHD-SBRT treatment in the RT reference centre (Institut J. Bordet) after review in a dedicated multidisciplinary oncological board (MOC). For a minimum of 5 days before the SBRT simulation, fiducial markers (PolyMark™ 0.8 × 3 mm, RT-IDea EU, Netherlands or preloaded gold markers EchoTip™ Ultra Fiducial Needle, Cook Medical, IN, USA) were inserted into the tumour (a minimum of one) under endoscopic ultrasonography guidance as described by Figueiredo *et al.*<sup>16</sup> In case of fiducial insertion failure, SBRT was not authorized for safety reasons. A minimum of 4 h fasting was required before CT simulation. Patients were immobilized in the supine position with their arms over the head. A four-dimensional (4D) CT scan was performed to assess respiratory motion. In case of fiducial respiratory motion in any direction of >5 mm, the use of an abdominal compressor (ZiFix™, QFix, Avondale, PA, USA) was mandatory. After a scan without contrast, a triphase contrast-enhanced CT simulation was performed followed by new-sequence acquisitions to assess the respiratory motion with the abdominal belt on. The gross tumour volume (GTV) was contoured on a 1 mm-slice thickness contrast-enhanced CT scan with a systematic review of the contouring by a specialized radiologist. The TVI structure included the whole circumference segment of major abdominal vessels (coeliac artery, common hepatic artery, portal vein, vena cava, superior mesenteric artery and/or superior mesenteric vein) in contact with the GTV or within 5 mm. To account for respiratory motion, an internal target volume (ITV) based on all the CT scan sequences available was created for both GTV and TVI. PTV1 encompassed the ITVs plus a 3 mm margin. The critical GI OARs (stomach, duodenum, colon and small bowel) were delineated on an individual loop basis. An automatic 3 mm expansion was then created and corrected

for additional respiratory motion on all the CT scan sequences available as a planning organ at risk volume (PRV) for each GI OAR. A protective PTV2 was created by subtracting the PRV<sub>total</sub> from the PTV1, and a PTV3 was generated to encompass the ITV<sub>TVI</sub> with an expansion of 3 mm. Elective nodes were not included in the treatment volume.

SBRT was delivered in five consecutive daily fractions. An IDP was applied and as per definition, the IDP was not based on the target volume but based on OARs tolerance levels to respect the following OARs dose constraints:<sup>13</sup> for PRV stomach, duodenum, colon and small bowel,  $D_{\max(0.5\text{cc})} < 35$  Gy,  $V_{30\text{Gy}} < 2$  cc; for PRV spinal cord,  $V_{20\text{Gy}} < 1$  cc; for kidneys,  $D_{\text{mean}} < 10$  Gy and  $V_{12\text{Gy}} < 25\%$ ; and for liver;  $D_{\text{mean}} < 15$  Gy and  $D_{700\text{cc}} < 21$  Gy. The target dose was individually maximized to the highest achievable level with simultaneous integrated boost to the PTV2 and particularly PTV3 up to  $D_{\max(0.5\text{cc})} < 53$  Gy.

All volumetric modulated arc therapy plans were designed using the Monaco™ planning system *via* the Monte Carlo algorithm for Elekta Infinity™ linear accelerators equipped with Agility™ (Elekta, Atlanta, GA, USA). All patients received prophylactic proton-pump inhibitors and antiemetic medication and a 4 h fasting period was required before each session. Daily cone beam CT (CBCT) was carried out before and after each treatment fraction.

#### *Restaging, surgery and follow up*

Early follow up with clinical assessment only was systematically performed on the last day of SBRT delivery and 2–4 weeks after the end of the SBRT. A full restaging was then performed 4–7 weeks after the completion of the iHD-SBRT and included clinical assessment, thoracic–abdominal CT scan, tumour marker (CA19.9) and optional abdominal MRI and PET-CT. After review in a centralized dedicated multidisciplinary oncological board, patients were evaluated for surgical exploration if no progression.

Surgery was performed in the reference surgical centre (Erasmus Hospital) at a maximum of 10 weeks after the end of the iHD-SBRT. Tumour resections were performed by laparotomy and consisted of either pancreaticoduodenectomy, total pancreatectomy or distal pancreatectomy with *en bloc* coeliac axis resection (modified

Appleby procedure). Pancreatectomies were associated with standard lymphadenectomy, and concomitant venous resection was performed in case of suspected tumoural venous involvement.

Follow-up examinations including at least clinical assessment, blood chemistries and thoracic–abdominal CT scan were then carried out every 3–4 months after the SBRT or oncological resection for the resected cases.

#### *Endpoints and statistical analysis*

The complete feasibility of the therapeutic sequence was evaluated and the iHD-SBRT-related acute and late toxicity data were collected during the follow up according to the common terminology criteria for adverse events version 4.0.<sup>17</sup> Acute toxicity was defined as occurring <6 months from SBRT completion, whereas late toxicity was defined as occurring  $\geq 6$  months after SBRT. For patients who had undergone an oncological resection, the appearance or worsening of acute toxicity which was undoubtedly attributed to the surgery was recorded as a postoperative complication but was not reported as iHD-SBRT-related acute toxicity. On the other hand, toxicity which could be partially induced by the SBRT was reported as iHD-SBRT-related toxicity.

The oncological outcomes included LC, progression-free survival (PFS, locoregional and distant), OS and (R0) resection rate (RR). The site of first failure was documented as systemic, locoregional failure (LRF) or mixed. Moreover, all LRFs were categorized as in field if the recurrence/progression occurred inside the isodose 25 Gy; while out-field recurrence was defined as any new lesion outside the 25 Gy isodose line. The 1-year LC rate after SBRT was defined as the proportion of patients in whom no radiological proof of local progression was described in comparison with the simulation contrast-enhanced CT scan. PFS was calculated from the date of the diagnosis (biopsy proven) to the date of the last follow up or locoregional/distant metastatic progression of disease. OS was calculated from the date of the diagnosis (biopsy proven) to the date of death; patients were censored at the date of last news if death was not observed. The resection rate was defined as the proportion of patients included who underwent a curative-intent resection and the R0 RRs were reported at 0 and >1 mm from the inked

margins. Histopathological response was graded according to the tumour regression grading of the College of American Pathologists (CAP).<sup>18</sup> Postoperative complications were also recorded.

Statistical analyses were performed using Stata 14. The normal distribution of the data was verified using histograms, boxplots, and quantile–quantile plots, and the equality of variances was checked using the Levene's test. Categorical data were described with percentages and numbers and continuous data were described with median and P25–P75. Since most continuous data followed an asymmetric distribution, we used non-parametric tests for all these variables, beginning with the Wilcoxon test to evaluate for differences between the medians (P25–P75) observed in the different groups. Regarding categorical data, chi<sup>2</sup> tests were used for the different analyses. Finally, survival functions for OS and PFS were plotted using the Kaplan–Meier method and compared by log-rank test. A *p* value of less than 0.05 was considered significant.

## **Results**

#### *Patient characteristics*

In total, 39 patients were eligible and included in this analysis. All baseline characteristics of the cohort are described in Table 1. The median age was 60.7 years [interquartile range (IQR) 52.2–67.7] and the median diameter of the tumour was 37 mm (IQR 32.0–44.0). The rates of BR and LAPC tumours were, respectively, 53.8 and 46.2%. The tumour was located in the pancreatic head in 89.7% (*n*=35) and in the body or tail in 10.4% (*n*=4). The median pretreatment serum levels of CA19.9 was 83 kU/l (IQR 17–210, *N*<37). Twenty-seven patients (69.2%) showed a direct tumoural gastrointestinal invasion (duodenum and/or stomach) at the initial radiological assessment. All 39 patients started an induction with mFFX, with a shift to Gem/nP in 2 patients. The median number of chemotherapy cycles was six (IQR six–eight) and the median duration of induction was 3.4 months (IQR 2.5–4.1 months). After restaging at the end of the induction chemotherapy and discussion in a centralized dedicated MOC: 2 patients showed a metastatic progression (5.1%), 7 had a partial response (18%) and 30 had a stable disease (76.9%). An endoscopic ultrasound was performed in the 37 non-progressive patients for the insertion of fiducials, mandatory

**Table 1.** Baseline characteristics of the intention-to-treat and SBRT cohort.

	Intention to treat (n=39)	SBRT (n=34)
Age, years, median (IQR)	60.7 (52.2–67.7)	60.2 (51.7–67.7)
Sex, male, n (%)	24 (61.5)	23 (67.6)
Tumour diameter, mm, median (IQR)	37.0 (32.0–44.0)	37.0 (32.0–44.0)
Type		
Borderline resectable, n (%)	21 (53.8)	18 (52.9)
Locally advanced, n (%)	18 (46.2)	16 (47.1)
Primary site		
Head/uncus/ithsmus, n (%)	35 (89.7)	31 (91.2)
Body/tail, n (%)	4 (10.3)	3 (8.8)
CA19.9 values (kU/l)		
At diagnosis, median (IQR)	83.0 (17.0–210.0)	78.0 (17.0–210.0)
Pre-SBRT, median (IQR)	/	53.9 (14.5–150.0)
Radiological tumoural GI invasion		
Yes, n (%)	27 (69.2)	23 (67.6)
No, n (%)	12 (30.8)	11 (32.4)
Clinical T stage*		
T1c (>1–2 cm), n (%)	2 (5.1)	2 (5.9)
T2 (>2–4 cm), n (%)	10 (25.7)	9 (26.5)
T3 (>4 cm), n (%)	7 (17.9)	4 (11.8)
T4 (involving CA/CHA/SMA), n (%)	20 (51.3)	19 (55.8)
Clinical N stage		
N0, n (%)	10 (25.6)	9 (26.5)
N+, n (%)	29 (74.4)	25 (74.4)
Type of induction chemotherapy		
mFFX, n(%)	37 (94.9)	32 (94.1)
mFFX followed by Gem/nP, n (%)	2 (5.1)	2 (5.9)
Number of cycles, median (IQR)	6 (6–8)	6 (6–8)
Time of induction (months), median (IQR)	3.4 (2.5–4.1)	3.4 (2.5–4.0)
*According to the AJCC TNM staging system, eighth edition. AJCC, American Joint Committee on Cancer; CA, coeliac artery; CHA, common hepatic artery; Gem/nP, gemcitabine/nab-Paclitaxel; GI, gastrointestinal; IQR, interquartile range; mFFX, modified fluorouracil, irinotecan and oxaliplatin; N, node; SBRT, stereotactic body radiation therapy; SMA, superior mesenteric artery; T, tumoural; TNM, tumour–node–metastasis.		

**Table 2.** Treatment plan analysis for the PTVs and related BED<sub>10</sub>.

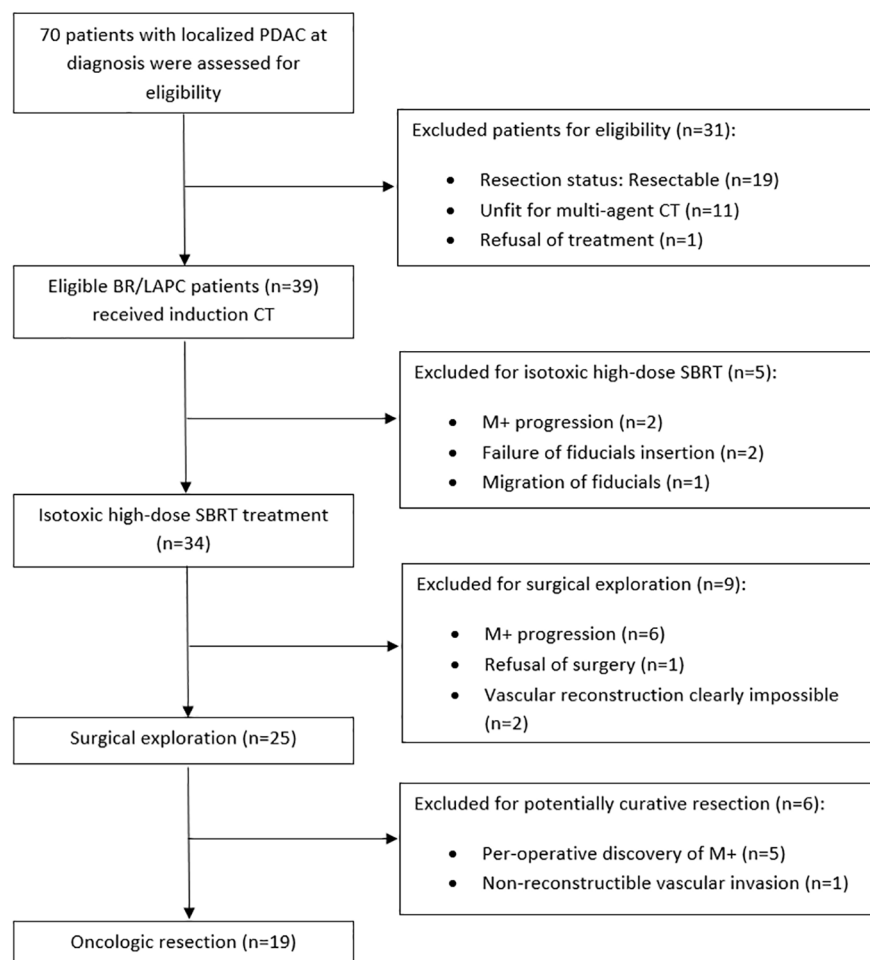
	Median volume, cm <sup>3</sup> (IQR)	Mean dose (Gy), median (IQR)	Related BED <sub>10</sub> (Gy), median (IQR)
PTV1	96.3 (74.9–117.7)	36.4 (35.0–38.5)	62.8 (59.5–68.2)
PTV2	71.3 (58.7–93.6)	40 (38.5–41.5)	72.4 (68.2–77.3)
PTV3	47.2 (35.2–56.2)	42.4 (40.9–44.5)	78.2 (74.4–84.1)
D <sub>max</sub>	/	51.9 (48.6–52.5)	105.6 (95.8–107.6)

BED<sub>10</sub>, biologically effective dose ( $\alpha/\beta=10$ ); D<sub>max</sub>, maximum dose; Gy, gray; IQR, interquartile range; PTV, planning target volume.

for the SBRT preparation. In two patients a technical failure of the fiducial insertion occurred and in one patient, the two inserted fiducials migrated and disappeared. Hence, for safety reasons, these

three patients were excluded from iHD-SBRT treatment and were directly referred to a surgical exploration.

For the 34 remaining patients (87.1%), an iHD-SBRT was successfully delivered after a median of 19 days (IQR 1–29 days) from the last cycle of chemotherapy, and no concurrent radiosensitizer was used. The PTVs and BED<sub>10</sub> related to the PTVs are described in detail in Table 2. After the end of the multimodal neoadjuvant sequence, 6/34 patients showed a metastatic progression (17.6%) at the pre-surgery restaging, 1 patient refused the surgical exploration and 2 LAPC patients were deemed ‘never resectable’ at MOC even with vascular reconstruction. As such, 25 patients were referred for a surgical exploration. The extended flowchart of the included patients is shown in Figure 1.



**Figure 1.** Flowchart of the included patients. BR, borderline resectable; CT, computed tomography; LAPC, locally advanced pancreatic cancer; M+, metastasis; PDAC, pancreatic ductal adenocarcinoma.

### Treatment-related toxicity

Acute and late SBRT-related toxicities are summarized in Table 3. The main acute toxicities were grade 1 or 2: fatigue (91%); flare-up abdominal pain (61.8%) for which a temporary increase of analgesics was required in seven patients; diarrhoea (32.3%); nausea (26.5%); gastroparesis (23.5%); and vomiting (14.7%). Grade 3 acute SBRT-related toxicities were reported in three patients and included grade 3 fatigue (5.9%,  $n=2$ ) and a short duodenal stenosis safely treated by echo-endoscopy (2.9%,  $n=1$ ). Late toxicities data (>6 months) are available for 24 patients. Grade 3 late toxicities were reported in one patient (4.2%) and consisted of an upper intestinal haemorrhage at the surgical site and was treated by clip endoscopic haemostasis. No acute or late grade 4 SBRT-related toxicities were reported.

### Surgical outcomes

In total, 25 patients (73.5%) were explored by laparotomy after the whole neoadjuvant sequence, of whom 19 patients [55.9% overall, 13/18 BR (72.2%) and 6/16 LAPC (37.5%)] underwent an oncological resection with curative intent. The surgical exploration was performed after a median duration of 46 days (IQR 34–60) from the end of SBRT. Six patients were not candidate for an oncological resection after surgical exploration due to the intraoperative discovery of liver metastasis ( $n=5$ ) and a locally non-resectable tumour ( $n=1$ ). Oncological surgical resection included pancreatoduodenectomy in 16 patients (84.2%), total pancreatectomy in 1 and distal pancreatectomy with *en bloc* coeliac axis resection in 2. Venous resection/reconstruction was required in 13 patients (68.4%). Direct intestinal invasion was pathologically proven in 11 patients (57.9%). The R0 RRs at 0 and >1mm were 73.7% ( $n=14/19$ ) and 26.3% ( $n=5/19$ ), respectively. Histopathological evaluation according to the CAP score showed a marked response in 1 patient (5.3%), a moderate response in 13 (68.4%) and poor or no response to the neoadjuvant sequence in 5 patients (26.3%). Adjuvant chemotherapy, mainly by mFFX, has been given in 73.7% of the resected patients ( $n=14/19$ ). Severe postoperative complications were seen in four patients (21%) in which one or several vascular reconstructions were required and included pancreatic fistula ( $n=1$ ), bleeding ( $n=2$ ), a portal thrombosis with temporary liver failure ( $n=1$ ) and severe gastroparesis ( $n=1$ ). The 100-day postoperative mortality was nil.

**Table 3.** Acute and late grade 2 and 3 SBRT-related toxicities.

	Acute ( $n=34$ )		Late ( $n=24$ )	
	Grade 2	Grade 3	Grade 2	Grade 3
Fatigue	9	2	2	–
Abdominal pain*	3	–	–	–
Nausea	1	–	–	–
Vomiting	1	–	–	–
Diarrhoea	2	–	–	–
Bloating	2	–	2	–
GI bleeding	–	–	–	1
GI stenosis	–	1	–	–

\*Appearance or worsening.  
GI, gastrointestinal; SBRT, stereotactic body radiation therapy.

### Oncological outcomes

The median follow up was 18.2 months (IQR 14.7–24.5, minimal follow up: 12 months) and at the last follow up, 19 patients were alive (48.7%). The median OS, 1-year and 18-month OS rates in the intention-to-treat population were, respectively, 24.5 months [95% confidence interval (95%CI) 18.0–32.3], 84.2% (95%CI 68.1–93.0) and 64.7% (95%CI 46.6–79.4%). For the patients who had completed iHD-SBRT, the median OS, 1-year and 18-month OS rates were, respectively, 24.5 months [95%CI 18.0–32.3 (BR: 22.9 (95%CI 16.0–32.3); LAPC: 24.5 months (95%CI 18.2–33.3),  $p>0.05$ )], 87.9% (95%CI 70.6–95.6) and 69.0% (95%CI 49.0–83.7), while for the patients who had also undergone an oncological resection, the results were 32.3 months (95%CI 22.9–43.4), 100% (95%CI 96.3–100.0) and 86.7% (95%CI 54.6–97.2), respectively. The median PFS for the intention-to-treat, SBRT and resected cohorts were, respectively, 15.4 (95%CI 7.9–24.1), 15.6 (95%CI 8.2–24.1) and 24.1 (95%CI 17.4–36.6) months. For the SBRT cohort, the median distant PFS was 29.0 (95%CI 6.5–43.4) months for the BR tumours and 9.9 (95%CI 7.8–17.5) months for the LAPC patients ( $p=0.15$ ). The median locoregional PFS for the SBRT cohort was not reached for both the BR and the LAPC groups. OS and PFS data are shown in Figures 2 and 3. After the IDP SBRT, the 1-year LC rate was 84.6% (95%CI 49.0–96.9) for the BR and 64.3% (95%CI 34.0–86.3) for the LAPC cohort ( $p=0.23$ ). IN total, 11 patients (34.4%) showed a locoregional relapse

**Table 4.** Incidence and pattern of failure distribution after SBRT ( $n=34$ ).

Pattern of failure	N (%)
At first progression	
Total of events	23/34 (67.6)
Distant only	16 (69.6)
Liver	12 (52.2)
Lung	5 (21.7)
Peritoneum	1 (4.3)
LR only	2 (8.7)
Mixed	5 (21.7)
Localization of all the reported LR events	11/34 (34.4)
In field	7 (20.6)
Out field	3 (8.8)
Mixed	1 (3)
LR, locoregional; SBRT, stereotactic body radiation therapy.	

after iHD-SBRT: 7 cases were in field (63.6%), 3 cases were out field (27.3%, including 2 relapses in the residual caudal pancreas after resection) and 1 case was a combination of in- and out-field failures (9.1%). The incidence and pattern of failure are reported in detail in Table 4.

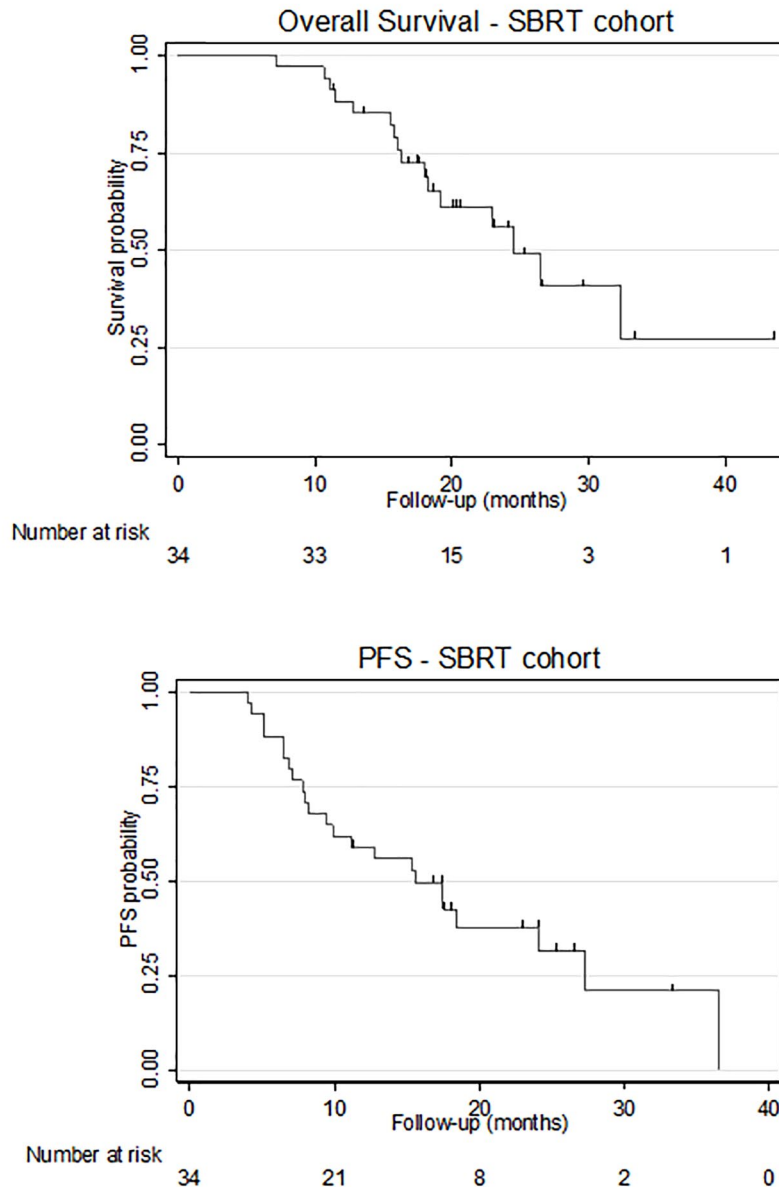
### Discussion

The SBRT approach has already shown interesting results regarding the LC and survival in BR and LAPC patients.<sup>8</sup> However, one of the main difficulties is to deliver a high dose to the tumour while properly sparing the adjacent GI OARs which are often directly invaded by the pancreatic tumour. Substantial expectations were placed upon the randomized phase II Alliance A021501 trial designed to compare the outcomes of BR patients treated with induction FFX alone or followed by SBRT (33 Gy in 5 fractions with SIB up to 40 Gy at TVI; or 25 Gy in 5 fractions).<sup>19</sup> Unfortunately, the study was suspended following an interim analysis of 30 patients revealing a crossing of the futility boundary for R0 RRs for the SBRT arm (<11 patients among 30 underwent an R0 resection). The results regarding the patients enrolled prior the closure were recently presented (70 patients enrolled in ARM A (FFX) and 56 in arm B (FFX + SBRT - underpowered)).

The primary endpoint, 18-months OS rate, was respectively 67.9 *versus* 47.3% in disfavour of the SBRT arm.<sup>20</sup> However, reducing the dose too much to ensure safety, as commonly done in current practice and also in the Alliance trial, is not optimal, as the fractionation schemes of 25–33 Gy in 5 fractions correspond to a maximum BED<sub>10</sub> of 55 Gy, well below the ablative doses sought with SBRT. It is therefore not surprising that the survival benefit usually obtained with this low-BED SBRT is null or modest and that the LC is weaker than that observed with the first historical SBRT analyses of non-randomized studies available.<sup>8</sup> As recently demonstrated by several studies, the delivery of high BED<sub>10</sub> to the tumour is indeed associated with a better survival and particularly, a BED<sub>10</sub> > 70 Gy seems to be a threshold to be crossed in order to obtain the best survival benefits.<sup>10–12</sup> To this purpose, the IDP based on OARs dose tolerance levels is a new technique of SBRT prescription particularly well adapted to the PDAC characteristics, allowing the delivery of high-dose SIB to the tumour while precisely controlling the risk of severe toxicities. To our knowledge, we are the first to integrate an IDP SBRT in a total neoadjuvant sequence with multiagent chemotherapy followed by a systematic surgical exploration in case of non-progression for BR and LAPC patients. Although PDAC tumours showing a radiological invasion of the duodenum and/or the stomach were excluded from the recent modern SBRT studies published,<sup>19–22</sup> this was not an exclusion criterion in our study. In this way, our study is closest to the real daily practice as tumoural direct invasion of the adjacent GI organs is frequent in PDAC.

The feasibility of our neoadjuvant sequence was very good since 87.1% of the patients were able to receive and complete the iHD-SBRT after induction by mFFX. This result emphasizes the fact that a high-dose SBRT can be easily integrated within a full neoadjuvant sequence. The iHD-SBRT treatment could be started quickly after the end of the last chemotherapy cycle (median time of 19 days) without any safety issues, minimizing the time without full-dose systemic treatment. Regarding the safety of the iHD-SBRT, as expected while using an IDP SBRT, the toxicity rates were highly favourable, even for the significant number of high-risk tumours invading the duodenum and/or stomach, with GI acute and late grade  $\geq 3$  toxicity rates under 5% (2.9% and 4.2% respectively). The other purpose of using an IDP SBRT is the delivery of an individualized



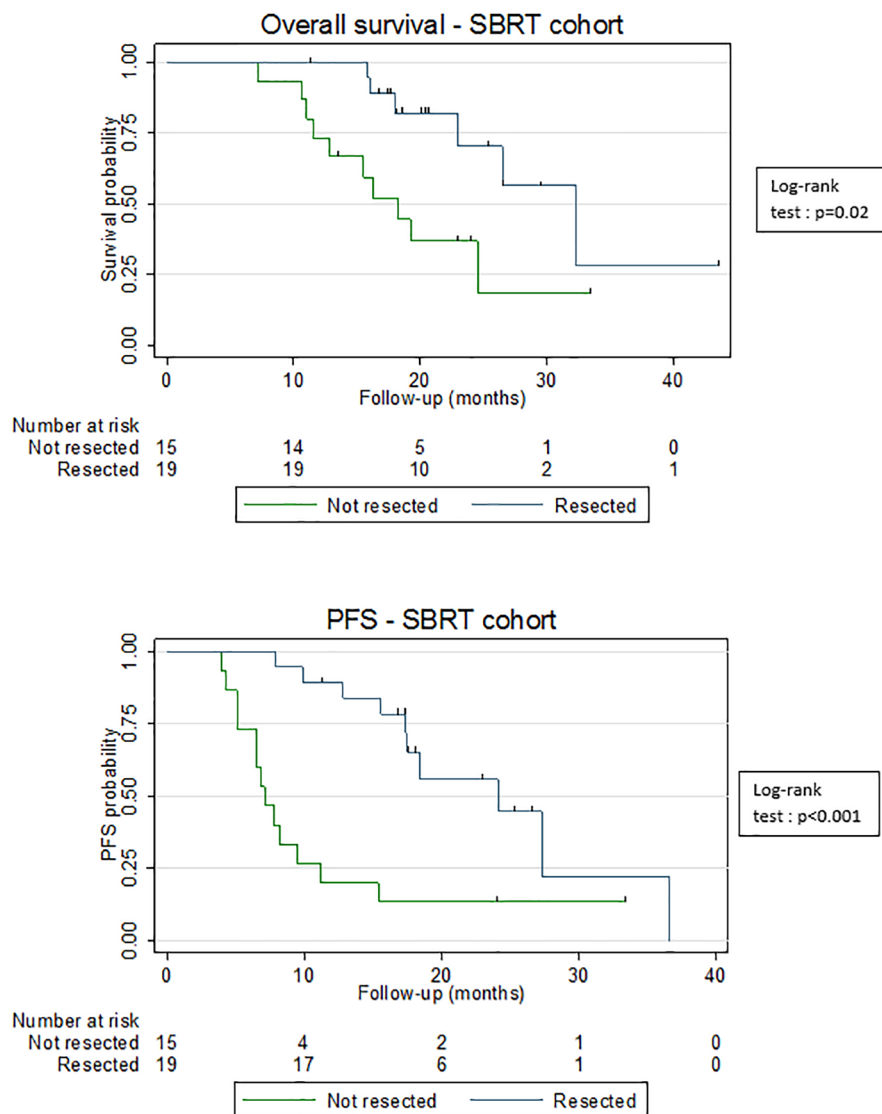


**Figure 2.** Kaplan-Meier plot of overall survival and progression-free survival (PFS) for the SBRT cohort ( $n=34$ ). SBRT, stereotactic body radiation therapy.

maximized dose to the tumour. This was also achieved as the median mean BED<sub>10</sub> delivered to the PTV2 (global PTV1 minus the PRV<sub>total</sub>) and the PTV3 [dedicated to the TVI's simultaneously integrated boost (SIB)] was, respectively, 72.4 Gy (68.2–77.3) and 78.2 Gy (74.4–84.1), crossing the 70 Gy threshold.

The resection rates after the whole neoadjuvant sequence were highly favourable when compared with the current results reported in the literature (Table 5), especially for the LAPC tumours (RR:

37.5%), for which the systematic surgical exploration seems to be beneficial. It is well known that a major issue with the use of modern multi-agent chemotherapy and RT is the difficulty in predicting the resectability by imaging assessment.<sup>23,24</sup> As it was also the case in our study, only a minority of patients (23.5%,  $n=8$ ) have shown a radiological improvement in the number and degree of TVIs after the whole neoadjuvant sequence due to insufficient differentiation of residual tumour *versus* desmoplasia, particularly at TVIs.<sup>23–25</sup> However, this does not always imply that a potentially



**Figure 3.** Kaplan-Meier plot of overall survival and progression-free survival (PFS) from the SBRT cohort: resected versus non-resected ( $n=34$ ). SBRT, stereotactic body radiation therapy.

curative resection will not be possible for the LAPC patients concerned as recently reported in the literature.<sup>26</sup> Likewise, for three of our LAPC patients without radiological regression of the non-reconstructable arterial tumour contact, multiple intra-operative negative biopsies around the arterial bed allowed for the final decision of an oncologic resection.

For the 19 PDAC resected, the R0 RR at 0 and >1 mm were 73.7% ( $n=14/19$ ) and 26.3% ( $n=5/19$ ), respectively, which is satisfactory, although lower than what is often reported in

the literature. This can be largely explained by the fact that a complementary immunohistochemistry staining was performed on the margins in a majority of the cases which led to the detection of residual isolated tumour cells by the pathologists. Another point to mention is the fact that for 36% ( $n=5/14$ ) of the patients resected with R1 margins at  $\leq 1$  mm, the margins were successfully cleared at the TVIs after SBRT, and the R1 resection was due to other margins (a circumferential or pancreatic margin). Finally, the burden of severe postoperative complications (21%,  $n=4/19$ ) was acceptable

**Table 5.** Comparison of our oncological outcomes with selected modern pancreatic SBRT trials available in the literature.

Study	Study design	N	Resection status	Dose (Gy)/#	RT machine	CT	Resection rate (%)	R0 resection rate, 0 mm (%)	LC (at 1 year, %)	Grade ≥ 3 GI toxicity (%)	Acute	Late	All	Median survival from diagnosis (months)	Res
Current study	Observational	18 16	BR LAPC	35–40/5 (SIB TVI up to 53Gy)	Linac	I: FFX (94.1%)–Gem/nP (5.9%; 6 cycles)	72.2 37.5	All: 73.7	All: 74.1 BR: 84.6 LAPC: 64.3	2.9	4.2		All: 24.5§ BR: 22.9 LAPC: 24.5	All: 32.3	
Chuong <i>et al.</i> <sup>27</sup>	Retrospective	57 16	BR LAPC	25–30/5 (SIB TVI 35–50Gy)	Linac	I: Gem based (3 cycles)	56 0	97 –	81 (not resected only)	0	5.3		16.4 15	19.3 –	
Herman <i>et al.</i> <sup>28</sup>	Phase II	49	LAPC	33/5	Linac	I: Gem (up to 3 weeks) C: gem	8	100	78	12.2	10		13.9	22.2	
Mellon <i>et al.</i> <sup>29</sup>	Retrospective	110 49	BR LAPC	28–30/5 (SIB TVI 50Gy)	Linac	I: Gem based or FFX	51 10	96 100	78 (not resected only)	2	7		19.2 15	All: 34.2	
Comito <i>et al.</i> <sup>30</sup>	Phase II	45	LAPC	45/6	Linac	I: Gem based (71%)	–	–	87	0	0		19	–	
Zhong <i>et al.</i> <sup>31</sup>	Retrospective	631	LAPC	40/5	NR	I (87%); NR	10.8	92	NR	NR	NR		13.9	NR	
Quan <i>et al.</i> <sup>32</sup>	Phase II	19 16	BR LAPC	36/3	NR	I: Gem/capecitabine (4 cycles)	53 12.5	All: 91.7	63 78	0	0		28.3 14.3	31 24.6	
Jung <i>et al.</i> <sup>33</sup>	Retrospective	95	LAPC	24–36 (median 28)/4	Linac	I (14%)/C (81%): Gem based or FFX	7.4	57	80	3.2	3.2		16.7	NR	
Kharofa <i>et al.</i> <sup>34</sup>	Phase II	15 3 R	BR	25/5 (SIB TVI 33Gy)	NR	I: Gem/nP or FFX (3 months)	All: 67	All: 92	50	0	0		All: 21	All: 31	
Suker <i>et al.</i> <sup>21</sup>	Phase II	50	LAPC	40/5	NR	I: FFX	12	100	Median: 20 months	10	NR		15	23	
Zhu <i>et al.</i> <sup>11</sup>	Retrospective	527 493	LAPC	Low BED: 37/5–8 High BED: 42/5–8	Cyberknife	I: – C: Gem/S1 (4–6 cycles)	NR	NR	NR	NR	NR		18.2 20.3	NR	
Katz <i>et al.</i> <sup>20</sup> (abstract)	Phase II	40	BR	25–33/5 (SIB TVI up to 40Gy)	Linac	I: FFX (7 cycles)	47.5	73.7	NR	NR	NR		17.1	NR	
Simoni <i>et al.</i> <sup>22</sup>	Observational	27 32	BR LAPC	25–30/5 (SIB TVI 50Gy)	Linac	I: FFX or Gem/nP (6–12 cycles)	88.9 34.4	57.1	79.7	0	0		All: 30.2	Not reached	

§For information, the median OS from SBRT: 20.5 months.

#Number of fractions.

BED, biologically effective dose; BR, borderline resectable; C, consolidation; CT, chemotherapy; FFX, FOLFIRINOX (fluorouracil, irinotecan and oxaliplatin); Gem, gemcitabine; Gem/nP, gemcitabine/nab-Paclitaxel; Gy, gray; I, induction; LAPC, locally advanced pancreatic cancer; LC, local control; Linac, linear accelerator; NA, not applicable; NR, not reported; OS, overall survival; Res, Resected; R, resectable; RT, radiation therapy; SBRT, stereotactic body radiation therapy; SIB, simultaneously integrated boost; TVI, tumour-vessel interface.

considering the number of vascular reconstructions (68.4%,  $n=13/19$ ) and was comparable with the complication rates reported after chemotherapy alone.<sup>35</sup>

The median survival for the SBRT cohort in our study was 24.5 months, which is very promising, particularly for the LAPC sub-group with an impressive median OS of 24.5 months. A detailed comparison of our oncological outcomes with recently published SBRT studies can be found in Table 5. As also reported in the literature,<sup>21,28,29,32,34</sup> our oncological outcomes of OS and PFS between resected *versus* non-resected patients were clearly statistically significant (OS: 32.3 *versus* 18.2 months,  $p=0.02$ ; PFS: 24.1 *versus* 7.1 months,  $p<0.001$ ), but our study design does not allow drawing of conclusions, as a control group is missing. For information purposes only, a comparison of the main surgical and oncological outcomes of our SBRT cohort with a historical small control group from the prospective NEOPAX-001 trial [ClinicalTrials.gov identifier: NCT01715142]<sup>36,37</sup> with comparable eligibility criteria for BR and LAPC patients, and induction with a multi-agent chemotherapy without SBRT is available in Supplemental Table 1. From the intention-to-treat cohort, 33.3% of the patients ( $n=13/39$ , including the discovery of perioperative occult metastasis in 5/13 patients) showed a metastatic progression during or early after the end of the neoadjuvant therapy, which is similar to other neoadjuvant sequences without SBRT.<sup>38</sup> After a median follow up of 18.2 months, the median locoregional PFS of the SBRT cohort was not reached for both BR and LAPC groups. After the iHD-SBRT, the 1-year LC rate was 74.1%, which is promising and comparable with the results in the literature. The comparison of the 1-year LC of the resected *versus* non-resected patients after iHD-SBRT was not statistically significant (82.4 *versus* 60%,  $p=0.20$ ). In a disease where up to 30% of the patients die from local progression alone,<sup>39</sup> these results underline the promising role of the local effect of the SBRT in PDAC. The localization of our locoregional failures after iHD-SBRT were also investigated and were mostly in-field relapses only (63.6%,  $n=7/11$ ) within an area correctly covered by the SBRT treatment ( $>25$  Gy in 5 fractions). Therefore, the potential issue of the limited volume irradiated with the SBRT technique compared with conventional chemoradiotherapy does not appear to be a limitation in this study.

This study had several limitations. Our study enrolled a relatively small sample size, including both BR and LAPC tumours which can potentially add heterogeneity to the outcomes measured. The number of cycles of induction chemotherapy was variable, although a minimal number was required; therefore, the time and intensity of the induction part was not uniform. Finally, the use of an IDP SBRT implies a heterogeneity of the dose delivered to the patients.

## Conclusion

In conclusion, the integration of iHD-SBRT into a whole neoadjuvant sequence followed by surgical exploration in case of no progression is feasible. The iHD-SBRT displays a safe GI toxicity profile, also for high-risk tumours with a direct radiological invasion of the duodenum and/or stomach and adequately allows the recently recommended delivery of a  $BED_{10}>70$  Gy. These data and our favourable surgical and oncological outcomes emphasize the need to further explore the role of SBRT in the neoadjuvant setting of PDAC. To this purpose, a randomized comparative phase II trial for iHD-SBRT (STREREOPAC) [EudraCT number: 2021-002354-84] is under preparation in the authors' academic institutions, and other SBRT trials are ongoing, such as the following randomized phase II/III trials: the SOFT-Preop [ClinicalTrials.gov identifier: NCT03704662], the BRPNCC-1 [ClinicalTrials.gov identifier: NCT03777462], the Stanford [ClinicalTrials.gov identifier: NCT01926197] and the SMART trial [ClinicalTrials.gov identifier: NCT03621644].<sup>8,40-43</sup>

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## Author contributions

CB: implemented the SBRT treatment, drafted and designed the manuscript.

JLE/MAB: participated to the NCCN classification of the tumours, evaluated the radiological response and performed a systematic review of the GTV contouring.

JC/JN/PL: dedicated pancreatic surgeons.

YG/TDG/AH/LM/PE/JLVL: participated to the recruitment, administration of chemotherapy, MOC and insertion of fiducials.

MH: contributed to the statistical analyses.

JN/DVG/JLVL: contributed to major review of the manuscript.

LM/JLV: contributed to concept supervision of the manuscript.

All authors reviewed and edited the manuscript, gave critical input and gave final approval for publication.

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The authors declare that there is no conflict of interest.

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### Supplemental material

Supplemental material for this article is available online.


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