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Scientific Article

Safety and Efficacy of Neoadjuvant SABR in Pancreatic Cancer: Effect of Magnetic Resonance Imaging–Guided Respiratory-Gated Adaptive Radiation Therapy

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Purpose: We aimed to evaluate the safety and efficacy of neoadjuvant SABR using magnetic resonance imaging–guided respiratory-gated adaptive radiation therapy (MRgRg-ART) in pancreatic cancer.

Methods and Materials: We performed a single-institution retrospective review in patients with pancreatic cancer who underwent neoadjuvant SABR followed by surgical resection. After neoadjuvant chemotherapy, those considered resectable by the multidisciplinary team received SABR over 5 consecutive days using MRgRg-ART. Factors associated with severe postoperative complications (Clavien-Dindo grade ≥III) and prognostic factors for overall survival were analyzed.

Results: Sixty-two patients were included in the analysis, with a median follow-up of 10.3 months. The median prescribed dose to the planning target volume was 50 Gy. Fifty-two (85.3%) patients underwent R0 resection, and 11 (18.0%) experienced severe postoperative complications. No factors were associated with the incidence of severe postoperative complications. There were 3 cases of locoregional recurrence, resulting in a 12-month local control rate of 93.1%. Elevated postoperative carbohydrate antigen 19-9 was significantly associated with poor overall survival in the multivariate analysis ($P = .037$).

Conclusions: Neoadjuvant SABR with 50 Gy using MRgRg-ART delivered to pancreatic cancer resulted in a notable survival outcome with acceptable toxicities. Further studies are warranted to investigate the long-term effects of this method.

Introduction

Pancreatic cancer is well known for its poor prognosis. To date, surgical resection with negative resection margins is the only means of achieving long-term survival and a potential cure, but only 15% to 20% of patients are

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considered candidates for surgery.[1] In borderline resectable pancreatic cancer (BRPC) and locally advanced pancreatic cancer (LAPC), neoadjuvant therapy is frequently used to control micrometastasis, reduce tumor size, and increase the probability of resection.

In the neoadjuvant setting, radiation therapy (RT) is incorporated with chemotherapy to maximize treatment efficacy by controlling the micrometastasis in the locoregional area.[2-4] The PREOPANC study has reported benefits of neoadjuvant chemo-RT in locoregional failure and R0 resection rate compared with immediate surgery followed by adjuvant chemotherapy in resectable pancreatic cancer (RPC) and BRPC.[5] Also, the LAP-07 trial has shown better locoregional control (LRC) in the neoadjuvant chemo-RT arm than the chemotherapy alone arm in LAPC.[6] Traditionally, conventionally fractionated RT was commonly used, which delivers radiation over 5 to 6 weeks to the pancreas and lymph node areas and thus irradiates surrounding radiosensitive gastrointestinal organs as well. In contrast, SABR takes only 1 to 2 weeks to deliver and allows highly conformal treatment to a small target volume. As a result, SABR conveys low rates of locoregional failure (LRF), minimizes the dose to surrounding normal tissues, and reduces the time interval from chemotherapy.[7]

Previous studies have reported that an escalation of the radiation dose in SABR for pancreatic cancer may improve LRF[8] and consequently proposed guidelines recommend doing so if resources to ensure safety are available.[9] In our institution, we used magnetic resonance imaging (MRI)-guided respiratory-gated adaptive RT (MRgRg-ART) as a modality for neoadjuvant SABR to patients with pancreatic cancer. This novel technique has the following features, which allow safe dose escalation. First, MRI provides excellent soft tissue resolution of intra-abdominal organs compared with computed tomography (CT) scans.[10] Second, daily adaptive recontouring and replanning enable the management of daily anatomic variations of organs at risk (OARs).[11] Third, cine MRI monitors the real-time motion of the tumor, allowing respiratory-gated RT.[12] These advantages of MRgRg-ART have been demonstrated in several retrospective studies.[13-15]

We conducted this retrospective review of clinical results to evaluate the safety and clinical outcomes of neoadjuvant SABR using MRgRg-ART in pancreatic cancer.

Methods and Materials

Patient selection and workup

The institutional review board approved this retrospective review and allowed access to the institutional database. Patients with nonmetastatic pancreatic cancer who underwent neoadjuvant SABR followed by surgical resection from September 2016 to February 2021 were queried from our institutional database. These patients underwent staging workup, which included comprehensive history taking, physical examination, serum levels of carcinoembryonic antigen and carbohydrate antigen 19 to 9 (CA19-9), pancreatic protocol CT scan, pancreatobiliary MRI scan, F-18 fluorodeoxyglucose positron emission tomography scan, and endoscopy-based biopsy. Patients considered unresectable by our multidisciplinary team received neoadjuvant chemotherapy. Those with resectable disease categorized by the National Comprehensive Cancer Network criteria were also included to receive neoadjuvant chemotherapy at the discretion of the physician and the multidisciplinary team.[9] After neoadjuvant chemotherapy, patients in whom arterial reconstruction became feasible in the celiac axis (CA) and common hepatic artery (CHA) and in whom arterial encasement was resolved in the superior mesenteric artery were evaluated as operable and went on to receive neoadjuvant SABR followed by surgical resection.[16]

Radiation therapy

SABR was delivered over 5 consecutive days by MRgRg-ART. MRgRg-ART with the MRIdian Cobalt-60 system (ViewRay Inc, Oakwood Village, OH) was used in cases that needed daily adaptation to avoid violation of the institutional OAR dose constraints in treatment planning.[13] Those who did not meet the OAR dose constraints or whose tumor could be deformed or tracked by the MRIdian Cobalt-60 system were included for treatment. If a tumor could not be tracked by the MRIdian it was either because of an abnormal respiratory cycle of the patient or unclear boundaries of the tumor.

In the patients treated with MRgRg-ART, the clinical target volume (CTV) was defined as pancreatic mass and vascular infiltration as seen on diagnostic imaging and simulation CT or MRI scans. Lymph nodes clinically visible at the time of RT planning were also included in the CTV, but the distant nodal area was excluded because dissection was possible. Also, major vessels such as CA, superior mesenteric artery, or CHA, which were adjacent to the gross tumor, were electively covered in the CTV. The CTV was uniformly expanded by 3 to 6 mm to form the planning target volume (PTV). OARs were expanded by 4 mm to make planning OAR volumes. The prescription dose to the overlapping portion of the PTV and planning OAR volumes, termed "PTV2," was restricted to 35 Gy. The rest of the PTV excluding the PTV2 was termed "PTV1" and was dose-escalated to 50 Gy. Fifty Gy in 5 fractions is equivalent to biologically effective dose 10 = 100 Gy, which is considered an ablative dose.[13] Figure E1 shows the target volumes and isodose lines of 1 case included in the current study. Daily MRIs were

acquired, and the target and OARs were adaptively contoured to compensate for interfractional variations. Intrafractional respiratory motion was managed by tracking the tumors on real-time sagittal cine MRIs. Treatment plans were reoptimized to fit the institutional OAR dose constraints (ie, maximum dose delivered to 1 cc of the OAR [D1cc] < 35 Gy for the stomach, duodenum, and small bowel; Table E1).

In daily adaptive RT, OARs were recontoured and real-time online planning was done to meet the dose constraints or to improve target coverage. Treatment was delivered immediately after planning. Because the plan changed daily, a quality assurance (QA) process was necessary to check whether the treatment was delivered as designed. At our institution, the principle for daily adaptive RT is to verify the daily plan with QA after the treatment. For the first 9 cases of daily adaptive RT at our institution, QAs were conducted after daily planning according to the aforementioned principle. Our institution uses the gamma index method and has set the criteria of 2% and 2 mm for dose difference and distance to agreement, respectively. This is considered suitable for treatment when the passing rate exceeds 90%. The average gamma passing rate for the 9 patients was 97.83%, and the standard deviation was 1.97%. Afterward, we assumed that the adaptive treatment plan was consistent and accurate, and omitted the QA from the daily planning.

Chemotherapy

Patients with unresectable, borderline, or high-risk resectable tumors received neoadjuvant chemotherapy. The neoadjuvant chemotherapy regimen consisted of: (1) a 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX)-based regimen and (2) gemcitabine and nab-paclitaxel. After surgical resection, most of the patients received adjuvant chemotherapy. The adjuvant chemotherapy regimen consisted of: (1) a gemcitabine-based regimen, (2) FOLFIRINOX-based regimens, and (3) 5-fluorouracil and leucovorin. The adjuvant chemotherapy regimen was chosen by considering the disease response, patient performance, and compliance to the neoadjuvant chemotherapy.

Surgical resection

Surgical resection was usually performed 1 to 2 weeks after SABR. For tumors of the head or uncinate process, pancreatoduodenectomy was performed, and for tumors located in the body or tail of the pancreas, distal pancreatectomy or radical antegrade modular pancreatosplenectomy was performed. Vascular resections were performed, when necessary, at the discretion of the surgeon. A pathologist with expertise in pancreatic cancer graded the tumor regression by neoadjuvant therapy using the College of American Pathologists cancer protocol. A negative resection margin was defined as the absence of tumor cells at the resection margin. Postoperative complications were graded using the system described by Dindo et al.[17] Severe postoperative complications were defined as Clavien-Dindo grade ≥III (ie, surgical complications needing surgical, radiologic, or endoscopic intervention).

Statistical analysis

Statistical analysis was done using SPSS 26.0 (IBM SPSS Statistics for Windows; IBM Corp, Armonk, NY). Student *t* test was used for continuous variables and the χ^2 test was used for categorical variables. The assumption of equal variance was tested for Student *t* test. Univariate and multivariate analyses were performed using logistic regression for severe postoperative complications and the Cox proportional hazard model for overall survival (OS). The assumption of proportionality was tested for the Cox proportional hazard model using the log-minus-log plots. OS and LRF were analyzed by Kaplan-Meier estimation and were compared by the log-rank test. Start of follow-up was defined as the date of the surgical resection, and patients who had more than 6 months of follow-up were included in the survival analysis.

Results

Patient and treatment characteristics

Table 1 describes the patient and treatment characteristics. A total of 62 patients (18 with RPC, 30 with BRPC, and 14 with LAPC) were included, with a median age of 63 years (range, 40-82 years). About two-thirds of the patients (69.4%) had tumors located in the uncinate process or head of the pancreas. Nine patients (14.5%) had nodal disease.

With respect to neoadjuvant chemotherapy, FOLFIRINOX was the most used regimen (82.3%), with a median of 9 neoadjuvant chemotherapy cycles (range, 4-34 cycles). Fifty-seven patients (91.9%) received adjuvant chemotherapy, with 26 patients (41.9%) treated with gemcitabine-based regimen and 21 patients (33.9%) with FOLFIRINOX.

RT specifics were as follows. The median value of the minimum dose that covered 95% of the gross tumor volume (GTV D95) was 52.6 Gy (range, 30.8-60.8 Gy). There were 58 patients with a GTV D95 higher than 45 Gy and 46 with a GTV D95 higher than 50 Gy, accounting for 93.5% and 74.2% of the total, respectively. The median value of the stomach D1cc was 31.7 Gy (range, 2.6-35.0

Table 1 Patient and treatment characteristics

Characteristic	n = 62	
Age, y, median (range)	63	(40-82)
Sex		
Male	32	51.6%
Female	30	48.4%
Charlson-age comorbidity index		
<2	14	17.7%
≥2	48	82.3%
Site		
Uncinate, head	43	69.4%
Body, tail	19	30.6%
Resectability (NCCN, 2021)		
Resectable	18	29.0%
Borderline resectable	30	48.4%
Locally advanced	14	22.6%
Tumor size, cm, median (range)	2.5	(1.3-9.0)
T stage		
T1	3	4.8%
T2	32	51.6%
T3	2	3.2%
T4	25	40.3%
N stage		
N0	53	85.5%
N1	9	14.5%
CA19-9, U/mL, median (IQR)		
Initial	262	(15-1129)
Postoperative	11.5	(4.0-34.0)
CEA, ng/mL, median (IQR)		
Initial	2.9	(1.9-5.0)
Postoperative	1.7	(1.1-2.3)
Neoadjuvant chemotherapy cycle, median (range)	9	(4-34)
Neoadjuvant chemotherapy regimen		
FOLFIRINOX	57	91.9%
Gemcitabine/nab-paclitaxel	2	3.2%
No chemotherapy	3	4.8%
Adjuvant chemotherapy cycle, median (range)	6	(1-16)
Adjuvant chemotherapy regimen		
Gemcitabine based	26	41.9%
FOLFIRINOX	21	33.9%
FL	10	16.1%
No chemotherapy	5	8.1%

(*continued on next page*)

Table 1 (*Continued*)

Characteristic	n = 62	
GTV, cc, median (range)	6.5	(1.2-62.7)
PTV, cc, median (range)	20.4	(4.9-100.1)
GTV D95, Gy, median (range)	52.6	(30.8-60.8)
PTV1 D95, Gy, median (range)	50	(30.0-51.0)
PTV2 D95, Gy, median (range)	35	(30.0-40.0)
Stomach D1cc, Gy, median (range)	31.7	(2.6-35.0)
Duodenum D1cc, Gy, median (range)	32.8	(5.1-40.4)
Small bowel D1cc, Gy, median (range)	31.8	(8.0-35.7)

Abbreviations: CA19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; FL = 5-fluorouracil and leucovorin; FOLFIRINOX = 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan; GTV = gross tumor volume; IQR = interquartile range; NCCN = National Comprehensive Cancer Network; PTV = planning target volume.

Gy). The median D1cc values of the duodenum and small bowel were 32.8 Gy (range, 5.1-40.4 Gy) and 31.8 Gy (range, 8.0-35.7 Gy), respectively.

Surgical characteristics and postoperative complications

Surgical and postoperative outcomes are listed in Table 2. Twenty-five patients (40.3%) received pancreatoduodenectomy, and 30 patients (48.4%) received distal pancreatectomy or radical antegrade modular pancreatosplenectomy. Twenty-seven patients (43.5%) received vascular resection or reconstruction. Superior mesenteric vein was the most frequently resected structure (in 18 cases). Portal vein, CA, and CHA was resected in 4, 3, and 5 cases, respectively. Details of the vascular resection and reconstruction are described in Table E2. Resection margins were negative (R0) in 52 patients (85.3%) and positive in 9 patients (14.7%). According to College of American Pathologists grade, which assesses the treatment response to neoadjuvant treatment, grade 0 (complete response) was achieved in 4 patients (6.5%).

Severe postoperative complications occurred in 11 patients (18.0%). The most common severe postoperative complication was fluid collection, which occurred in 6 patients (9.7%). Other complications included wound dehiscence (n = 2), ascites (n = 2), and anastomosis site edema (n = 1). The details of postoperative complications, regardless of severity, are listed in Table E3. Large PTV (>5cc) was associated with severe postoperative complications in the univariate analysis (P = .037). However, there was no factor associated with severe postoperative complications in the multivariate analysis, including high OAR D1cc (>35 Gy; P = .410) or large PTV (>5cc; P = .113) (Table 3).

Survival and patterns of failure

The median postoperative follow-up duration was 10.3 months (range, 0.6-27.8 months) for all patients and 12.7 months (range, 6.0-27.8 months) for patients with more than 6 months of follow-up after surgery. All the survival and failure analyses were conducted on patients with more than 6 months of follow-up after surgery. As shown in Fig. 1B, the 12- and 18-month OS rates were 95.5% and 83.5%, respectively, and the LRF rates at the same time points were 6.9% and 6.9%, respectively. The survival outcomes according to the resectability criteria are described in Table E4 and Fig. E2. There was no significant difference in the survival outcomes between patients grouped by resectability criteria. There were 3 cases of locoregional failure and 13 cases of distant metastases. Locoregional failure without distant failure was observed in 1 case. In the 3 cases of locoregional failure, with respect to the radiation field, 1 in-field recurrence was in the common hepatic lymph node. Common sites of distant metastasis were the liver (n = 7) and peritoneum (n = 3).

The univariate analysis revealed that elevated postoperative CA19-9 (95% CI, 1.45-43.92; P = .017) was significantly associated with poor OS, and positive resection margin was associated with marginal significance (95% CI, 0.96-34.48; P = .056). The multivariate analysis showed that elevated postoperative CA19-9 (95% CI, 1.13-67.63; P = .037) was significantly associated with poor OS (Table 4), but resection margin status lost its association with OS (95% CI, 0.05-15.03; P = .934).

Discussion

To the best of our knowledge, this study is one of the earliest to report on the outcomes of postoperative

Table 2 Surgical and pathologic characteristics

Characteristic	n = 62	
Type		
PD/PPPD	25	40.3%
DP/RAMPS	30	48.4%
TP	7	11.3%
Methods		
Open	54	87.1%
Laparoscopic/robotic	8	12.9%
Estimated blood loss, cc, median (range)	650	(70-3150)
Operation time, min, median, (range)	265	(110-510)
Vascular resection		
Yes	27	43.5%
No	34	56.5%
Resection margin		
Negative	52	85.3%
Positive	9	14.7%
Perineural invasion		
Yes	43	70.5%
No	18	29.5%
Vascular invasion		
Yes	17	72.1%
No	44	27.9%
Treatment response (CAP grade)		
0	4	6.5%
1	12	19.4%
2	27	43.5%
3	16	25.8%
Not reported	3	4.8%
Postoperative hospital stay, d, median (range)	9	(6-42)
Postoperative complication, C-D grade ≥3	11	18.0%
Postoperative complication (C-D grade)		
1	5	8.1%
2	2	3.2%
3a	8	12.9%
3b	1	1.6%
4	2	3.2%

Abbreviations: CAP = College of American Pathologists; C-D = Clavien-Dindo; DP = distal pancreatectomy; PD = pancreatoduodenectomy; PPPD = pylorus preserving pancreatoduodenectomy; RAMPS = radical antegrade modular pancreatosplenectomy; TP = total pancreatectomy. Numbers may not add up because 1 patient received surgery at another institution.

complications of neoadjuvant SABR in pancreatic cancer treated with MRgRg-ART. MRgRg-ART was used in all the cases, and 50 Gy was prescribed to the PTV, which is higher than that of previous studies.[3,18-20] The incidence of severe postoperative complications was low, occurring in 11 (18.0%) patients, and properties of RT such as PTV and OAR dose showed no association with severe postoperative complications. The survival outcomes were noteworthy, with 12-month LRF and OS rates of 6.9% and 95.5%, respectively.

Table 3 Univariate and multivariate analysis of factors contributing to severe postoperative complication (Clavien-Dindo grade ≥3)

		Univariate analysis			Multivariate analysis		
Characteristic	**Severe complication rate**	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Charlson-age comorbidity index				.188			.501
<2	30.8%	1	0.63-10.82		1	0.30-11.84	
≥2	14.6%	2.60			1.88		
Resectability				.679			.911
RPC, BRPC	19.2%	1	0.27-7.50		1	0.17-7.06	
LAPC	14.3%	1.42			1.11		
OAR D1cc				.927			.518
<35 Gy	18.2%	1	0.12-10.58		1	0.18-31.69	
>35 Gy	16.7%	1.11			2.36		
PTV				.037			.126
<25 cc	11.4%	1	1.09-16.62		1	0.71-15.69	
>25 cc	35.3%	4.25			3.34		
Vascular resection				.416			.632
No	20.6%	1	0.17-2.58		1	0.16-3.09	
Yes	14.8%	0.67			0.69		
Estimated blood loss				.451			.566
≤700 cc	14.7%	1	0.45-6.16		1	0.35-6.75	
>700 cc	22.2%	1.66			1.54		
Operation time				.583			.793
≤240 min	14.3%	1	0.35-6.38		1	0.25-6.08	
>240 min	20.0%	1.5			1.24		

Abbreviations: BRPC = borderline resectable pancreatic cancer; LAPC = locally advanced pancreatic cancer; OAR = organ at risk; OR = odds ratio; PTV = planning target volume; RPC = resectable pancreatic cancer.

In SABR or hypofractionated RT, MRgRg-ART is being widely used in pancreatic cancer for its potential to safely deliver ablative doses.[13] At our institution, from the first trial of MRgRg-ART in the neoadjuvant setting, we prescribed 50 Gy to PTV1 and 33 to 35 Gy to PTV2 by using the simultaneous integrated protection technique to lower normal organ toxicities, including the gastrointestinal tract. Moreover, we performed surgery shortly after SABR in an attempt to minimize the difficulty of surgery caused by radiation-related fibrosis and

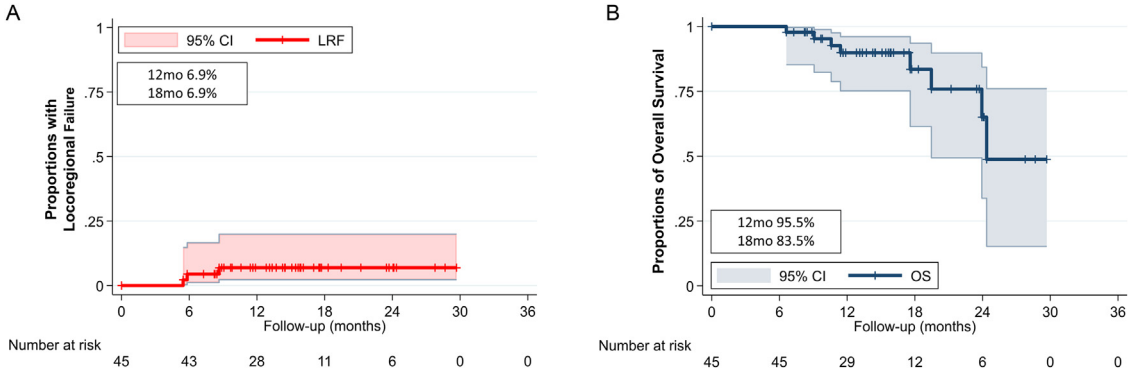

Figure 1 Kaplan-Meier curve of (A) locoregional failure and (B) overall survival of patients with more than 6 months of follow-up. *Abbreviations:* LRF = locoregional failure; OS = overall survival.

Table 4 Univariate and multivariate analysis of factors contributing to overall survival

	Univariate analysis			Multivariate analysis		
Characteristic	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Charlson-age comorbidity index			.373			.269
<2	1	0.41-10.73		1	0.32-57.08	
≥2	2.1			4.3		
Resectability			.505			.729
RPC, BRPC	1	0.39-6.96		1	0.25-7.47	
LAPC	1.64			1.35		
Postoperative CA19-9			.017			.037
Normal	1	1.45-43.92		1	1.13-67.63	
Elevated	7.97			8.77		
Severe postoperative complication			.462			.830
C-D grade <3	1	0.35-9.82		1	0.11-16.49	
C-D grade ≥3	1.86			1.32		
Resection margin			.056			.934
Negative	1	0.96-34.48		1	0.05-15.03	
Positive	5.74			0.89		

Abbreviations: BRPC = borderline resectable pancreatic cancer; CA19-9 = carbohydrate antigen 19-9; C-D = Clavien-Dindo; HR = hazard ratio; LAPC = locally advanced pancreatic cancer; RPC = resectable pancreatic cancer.

to minimize the chemotherapy-off duration and potential acute RT toxicities.

R0 resection is a well-known prognostic factor for pancreatic cancer.[21-23] Preoperative treatment in BRPC or LAPC may downsize tumors and enable surgical resection with an increased probability of R0 resection.[5,24] Of the 61 patients with available pathologic data, 52 (85.3%) had R0 resection. This rate is lower than that of previously published retrospective series studying the efficacy of neoadjuvant SABR, which reported R0 resection rates of over 90%.[3,4,18-20,25] However, the role of neoadjuvant SABR is not limited to achieving R0 resection; it also has a role in achieving tumor control in areas difficult to access by surgical means. The current study demonstrated good survival outcomes despite the relatively low R0 resection rate, suggesting a role beyond achieving R0 resection in neoadjuvant SABR. This may be explained by the short interval between neoadjuvant SABR and surgical resection, providing less time for the tumor to regress to achieve R0 resection. Also, the intensive chemotherapy regimen used before SABR could have contributed to the outcome, because a previous study stated that a regimen like FOLFIRINOX leads to less distant failures and improved survival.[26] This would also explain the high rates of perineural invasion (PNI) (70.5%) and vascular invasion (VI) (27.9%). The PREOPANC trial reported rates of PNI and VI of 39% and 19% in the preoperative chemo-RT arm, respectively. However, high rates of PNI and VI did not necessarily translate into worse oncologic outcomes.

In the PREOPANC trial, RPC and BPRC patients were included and were randomized to preoperative chemoradiation and immediate surgery groups. The rates of severe postoperative complications were 37.9% and 30.6% in the preoperative chemo-RT and immediate surgery groups, respectively.[27] A retrospective study by Blair et al[28] reported a severe postoperative complication rate of 23.0% after neoadjuvant chemoradiation with SABR of 33 Gy in 5 fractions. Another retrospective study reported 33% of postoperative complications above grade 3 after SABR of 36 Gy delivered in 3 fractions.[19] Zakem et al[18] reported the lowest severe postoperative complication rate of 8.2% (6 of 73 patients) with SABR delivered in up to 30 to 33 Gy in 5 fractions. In this study, 11 (18.0%) patients experienced severe postoperative complications. In the current study, a higher dose of 5 fractions of 10 Gy was prescribed compared with the PREOPANC study (15 fractions of 2.4 Gy) and other retrospective studies dealing with neoadjuvant SABR. We think it is because of the advantages of the MRgRg-ART and the experienced surgeons that a comparable rate of complication was achieved despite a higher dose of radiation. In the univariate analysis, none of the clinicopathologic factors, including high Charlson-age comorbidity index, high OAR dose, and large PTV, were associated with an increased rate of postoperative complications. The application of respiratory gating and daily adaptive therapy may play a role in keeping the radiation-related toxicity to a tolerable level even in patients with high OAR dose and large PTV.

Table 5 Previous and current studies of pancreatic cancer treated with neoadjuvant SABR

Study	Year	N*	Resectability	Dose/fractionation	Median follow-up (mo)	12 mo LRC (%)	12 mo OS (%)	Median OS (mo)
Chuong et al[4]	2013	32	BRPC, 32	35 Gy/25 Gy/5 fx	10.5	100	84.2	19.3
Mellon et al[3]	2015	61	BRPC, 56 LAPC, 5	40 Gy/30 Gy/5 fx	14.0	-	-	34.2
Chapman et al[20]	2018	38	BRPC, 31 LAPC, 7	30 Gy	20.0	68.4 (crude)	97.3	26.9
Quan et al[19]	2018	12	BRPC, 10 LAPC, 2	36 Gy/3 fx	15.4	-	100	24.6
Barrord et al[25]	2020	43	RPC, 6 BRPC, 37	SABR: 33 Gy/25 Gy/5 fx CFRT: 50.4 Gy/28 fx	18.5	SABR: 62 CFRT: 86 (LRFS)	-	-
Zakem et al[18]	2021	73	BRPC, 63 LAPC, 10	30 Gy	25.0	88 (crude)	-	-
Current study	2021	62	RPC, 18 BRPC, 30 LAPC, 14	50 Gy/35 Gy/5 fx	10.3	93.1	95.5	24.4

Abbreviations: BRPC = borderline resectable pancreatic cancer; CFRT = conventionally fractionated radiation therapy; LAPC = locally advanced pancreatic cancer; LRC = locoregional control; OS = overall survival; RPC = resectable pancreatic cancer; LRFS = locoregional failure-free survival.
*Patients who underwent surgical resection.

In the current study, vessels with tumor infiltration were included in the CTV, and more than 40% of patients received vascular resection after that. The safety of this intensive treatment toward vessels in the abdomen has not been verified, and there is a concern about it. One retrospective study, which excluded vessels in the CTV and with less frequent vascular resection, reported a greater rate of severe complications than the current study.[28] There are data that reported the rate of major hemorrhagic events as high as 20%.[29] Nevertheless, there are data including the current study that report vascular toxicities of less than 5% as postoperative complication.[28] Previously published guidelines on SABR to pancreatic cancer do not provide dose constraints to vascular structures.[3,30] The SABR dose constraints to vessels could be extrapolated from the thorax, assuming that the radiation tolerance of the endothelium is similar to that of the abdomen.[30] It is hard to conclusively state the safety with the given data. We think that such intense treatment to the vessel does not significantly increase the risk of major vascular toxicities and gives the chance of curative treatment to high-risk patients. Also, such a treatment approach should be carried out with caution in an institution with a well-organized multidisciplinary team.

The ultimate aim of neoadjuvant chemotherapy and SABR followed by surgical resection is to improve the LRF and OS. Previous studies of neoadjuvant SABR for pancreatic cancer with 12-month OS and LRC rates of patients who underwent surgical resection are listed in Table 5. The 12-month OS rate ranged from 84.2% to 100%, and the LRC rate ranged from 62% to 100%. The median OS rate ranged from 19.3 to 34.2 months.[4,19,20] Despite the high proportion of LAPC patients compared with the studies mentioned, the 12-month OS and LRF rates were 95.5% and 6.9%, and this may be attributable to the high dose prescribed.

This study had several limitations. First, given its retrospective nature, this study had an inherent potential for selection bias. For instance, some high-risk RPC patients who had superior mesenteric vein or PV abutment or nodal disease were included, and this patient population might have had a positive influence on the survival outcome. Second, this study had a heterogeneous patient population in terms of tumor resectability (RPC, n = 18; BRPC, n = 30; LAPC, n = 14). This heterogeneity makes it difficult to interpret and apply the results of this study in clinical practice. Third, in the grading of tumor regression, there is an ongoing issue of interobserver discordance and the prognostic value of the current reporting systems.[31] To date, no standardized or widely accepted tumor regression grading system has been established. Lastly, the follow-up was relatively short, with a median of 10.3 months, and the sample size was too small to result in a convincing conclusion. With longer follow-up and larger sample size, there is a potential to detect late toxicities induced from RT or surgical resection and to find out significant long-term oncologic outcomes. However, based on the results of this pilot study that confirmed the efficacy and safety of preoperative SABR for pancreatic cancer, it is expected that meaningful results will be obtained if the study is continued with a large number of patients.

Conclusion

Fifty gray in 5 consecutive fractions delivered to patients with pancreatic cancer in a neoadjuvant setting using MRgRg-ART resulted in notable survival outcomes with acceptable toxicity profiles. This novel method may be an option to deliver ablative doses of radiation in a short period of time to achieve LRF in such a treatment setting. Further studies with larger sample sizes and longer follow-up are warranted to investigate the long-term effects.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101312.

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