ORIGINAL ARTICLE

Radical antegrade modular pancreatosplenectomy for all pancreatic body and tail tumors: rationale and results

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Abstract

Background Radical antegrade modular pancreatosplenectomy (RAMPS) has been propagated as the standard of care for pancreatic cancers involving the body and tail of the pancreas. This procedure has been shown to have promising results in enhancing the microscopically negative tangential resection margins as well as the lymph node yield.

Methods This is a retrospective analysis of prospectively maintained database on the resections performed for all pancreatic body and tail tumors at Tata Memorial Centre.

Results Sixty-five patients underwent RAMPS without any perioperative mortality. The various pathologies comprised of adenocarcinoma (41.5%), neuroendocrine tumors (12.3%), solid pseudopapillary epithelial neoplasm (15.3%), cystic neoplasms (15.2%), etc. The R0 resection rate was 87.7%. Among this cohort, 27 patients had pancreatic adenocarcinoma. The 3-year OS and DFS for distal pancreatic cancers were 56% and 38%, respectively, but 3-year OS and DFS for other distal pancreatic tumors were 97% and 73%, respectively. On multivariate analysis, R0 resection significantly improved disease-free survival ($p = 0.023$) for pancreatic cancer.

Conclusion RAMPS procedure aids to achieve high negative tangential margins for all tumors involving the body and tail of the pancreas and not just pancreatic cancer in isolation. Since preoperative histologic diagnosis is not routinely indicated and also a number of other distal pancreatic tumors carry a relatively better prognosis compared with pancreatic cancer, our results provide further evidence that RAMPS should be considered as the procedure of choice for all operable tumors involving body and tail of the pancreas.

Keywords Distal pancreatosplenectomy · Radical antegrade modular pancreatosplenectomy · Pancreatic tumors

Introduction

In a seminal report by Strasberg et al. in 2003, radical antegrade modular pancreatosplenectomy (RAMPS) has been described as a modified form of distal pancreatosplenectomy for resections of cancers involving the body and tail of the pancreas [1]. The propagated advantages of this procedure included the high tangential margin negativity since the posterior dissection plane lies posterior to the anterior renal fascia and also the high lymph nodal yield that leads to better staging. This procedure has shown to yield good long-term survival benefits in a limited cohort in many reports although distal cancers are rather uncommon as compared with pancreatic head malignancy [2]. The characteristic feature of this procedure includes the dissection that proceeds from right to left with early vascular control and also lymphadenectomy being conducted based on the described lymphatic drainage of the region [3]. The purpose of this article is to study the perioperative and long-term survival outcomes of patients undergoing this procedure at the Tata Memorial Centre.

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Methods

This is a retrospective analysis of a prospectively maintained database of patients treated for all tumors involving

the body and tail of the pancreas. The relevant data from 2007 until 2016 were entered in a prospectively maintained database. It was retrieved from the electronic medical records of the Tata Memorial Centre and the follow-up data from standard protocols at the institute. The data included details collected from operative notes, anesthesia records, histopathology details, and follow-up visits. The preoperative workup of the patients with distal pancreatic tumors included tumor markers, baseline investigations, and pancreatic protocol contrast-enhanced computed tomography (CECT) and chest CT scan. The management of these patients was discussed in a dedicated multidisciplinary hepato-pancreato-biliary oncology team comprising of surgeons, medical oncologists, radiation oncologists, radiologists, and anaesthesiologists before planning for surgery. In this cohort, staging laparoscopy was performed selectively in cases where tumor marker CA 19-9 was elevated. The decision to perform surgery by minimally invasive approach (laparoscopic or robotic) was at the discretion of the operating surgeon. The posterior margin is guided by the preoperative CT scan that showed the relation of the tumor to the adrenals. When a rim of normal pancreas remained posterior to the tumor, anterior RAMPS was performed where a right to left approach is undertaken with the plane of dissection being posterior to the anterior renal fascia. In this dissection, the left adrenal vein was the intraoperative guide which was identified and traced retrograde to the left adrenal gland. When the tumors appeared to be in contact or close to the posterior capsule of the pancreas, posterior RAMPS was performed where the plane of dissection lies posterior to the left adrenal vein and left adrenal gland was removed for margins. The pathological assessment of the specimen had been done in accordance with the synoptic reporting with appropriate diligence rendered for the histology, pancreatic cut margins, tangential margins, lymph node yield, pancreatic intraepithelial neoplasia, lymphovascular invasion, and perineural invasion. The data on postoperative complications such as postoperative pancreatic fistula (POPF) was classified and documented in accordance with the ISGPF classification [4] and other complications have been documented based on Clavien-Dindo grading [5]. The details of adjuvant therapy and the recurrence data were retrieved and analyzed. The overall and disease-free survival was calculated for pancreatic cancers and other pancreatic tumors. The overall survival denotes the time period from the procedure until death due to any cause and disease-free interval denotes the time interval from the procedure until death or recurrence. The survival estimates were calculated using the Kaplan-Meier method. Univariate and multivariate analyses have been performed over the overall and disease-free survival functions using log-rank test and Cox proportional hazards model. All statistical analyses were performed using SPSS version 20.

Results

In this series, 65 patients with lesions involving the body and tail of the pancreas underwent RAMPS. The baseline characteristics and perioperative outcomes are shown in Table 1. The median American Society of Anaesthesiologists (ASA) score was 2. Out of the 65 patients, 17 (26.2%) underwent multivisceral resections involving colonic and gastric wedge resection. There was no 30-day perioperative mortality or in-hospital deaths, and one documented mortality within 90 days. Clinically relevant postoperative pancreatic fistula (CR-POPF) was observed in 17 patients (26.1%) (POPF-B in 16 patients and POPF-C in 1 patient) and only biochemical POPF-A was observed in 6 patients (9.2%). Among the 65 patients, other complications such as local collections occurred in 4 patients, septic shock in 1 patient, wound infection in 2 patients, respiratory complications in 1 patient, cardiac complication in 1 patient, and reoperation for bleeding in 3 patients and for bowel gangrene in one patient. Interventional radiologic procedures including pigtail insertion were done in 18 patients for managing various complications such as local collections and CR-POPF. The various final histopathology comprised adenocarcinoma (41.5%), neuroendocrine tumors (12.3%), solid pseudopapillary epithelial neoplasm (15.3%), cystic neoplasms (15.2%), gastrointestinal stromal tumors

Table 1 Characteristics of the patients ($N = 65$)

S.No	Characteristic	$N = 65$	%, range
1	Age (median)	54	19–90
2	Gender		
	Male	35	53.8%
	Female	30	46.2%
3	Surgery		
	Open RAMPS	58	89.2%
	Laparoscopic RAMPS	5	7.7%
	Robotic RAMPS	2	3.1%
4	Multivisceral resections	17	26.2%
5	Surgery duration (median)	300 mins	150–720 mins
6	BMI (median)	23.8	15–34.2
7	Blood loss (median)	850 ml	50–6500
8	CR-POPF rates	17	26.1%
9	Median hospital stay	10 days	4–51 days
10	Mean Tumor size	6.5 cm	0.8–20 cm
11	Histology		
	Adenocarcinoma	27	41.5%
	Neuroendocrine tumors	8	12.3%
	Serous cystadenoma	6	9.2%
	SPEN	10	15.3%
	Mucinous cystadenoma	4	6%
	Miscellaneous	10	15.3%

(1.5%), leiomyosarcoma (1.5%), adrenocortical carcinoma (1.5%), liposarcoma (1.5%), and benign pathology (3%). The overall R0 resection rate was 87.7%. Among this cohort of 65 patients, 27 patients had adenocarcinoma of pancreatic origin. The R0 resection rate for pancreatic adenocarcinoma was 85.2% and 89.5% for other distal pancreatic tumors. In these 27 patients with pancreatic cancer, the mean nodal yield was 6.7 whereas the mean nodal yield was 6 for other distal pancreatic tumors. The median CA19-9 value was 192 U/L. Among these 27 patients, 7 patients (26%) had nodal metastases. With respect to the T stage, 2 patients (7.4%) had T1 lesion, 17 patients (63%) had T2 lesion, 6 patients (22.2%) had T3 lesion, and 2 patients (7.4%) had T4 lesions. With respect to the grade of differentiation, the tumor was well differentiated in 4 patients (14.8%), moderately differentiated in 11 (40.7%), and poorly differentiated in 6 (22.2%). Among the 27 patients, lymphovascular invasion was noted in 5 patients (18.5%) and perineural invasion was noted in 12 patients (44.4%). There was no pancreatic intraepithelial neoplasia noted in any of these cases. Adjuvant chemotherapy was administered in 13 patients (48%). The chemotherapeutic regimen administered was gemcitabine in 9 patients, GEMCAP in 1 patient, and FOLFIRI in 1 patient. During the follow-up, recurrence was observed in 9 patients (33%). Out of which, 2 patients had local recurrence and the rest had distant metastases including 2 patients with both local as well as distant recurrence. The distant recurrences manifested as liver metastases, peritoneal disease, and 1 patient developed lung metastases. The 3-year OS and DFS for pancreatic cancers were 56% and 38%, respectively, and 3-year OS and DFS for other distal pancreatic tumors were 97% and 73%, respectively. On univariate analyses of various prognostic factors affecting overall survival and disease-free survival for distal pancreatic cancers, the margin status ($p = 0.014$, 95% CI 9.5–28.4), perineural invasion ($p = 0.048$, 95% CI 9.3–18.6), and tumor differentiation ($p = 0.019$, 95% CI 8.7–19.2) were noted to be significant prognostic factors for disease-free survival (Table 2). On multivariate analysis, margin status (R0 vs R1) remains the most important prognostic factor determining disease-free survival ($p = 0.023$, 95% CI 1.24–17.83) in patients undergoing resections for cancers involving pancreatic body and tail.

Discussion

The conventional technique of distal pancreatosplenectomy for tumors involving the body and tail of the pancreas has been in vogue for over many years and it has been pertinently observed that the incidence of recurrences has been noted to be high following resection of these uncommon cancers with poor 5-year survival ranging from 0 to 25% [6–8]. As the standardization for the surgical techniques evolved for

pancreatoduodenectomy [9], the obvious improved surgical outcomes encouraged similar principles to be extended for resectional procedures involving pancreatic body and tail cancers. Also, these distal pancreatic cancers have been known to be aggressive malignancies with poor survival and the only chance of cure has been a radical surgical resection with negative margins and adequate lymphadenectomy [10].

In the current series, using the principle of RAMPS, the negative tangential margins could be obtained in 87% of cases although the mean tumor size was 6.5 cm in the entire cohort. In an early report [11], the authors could manage to obtain negative tangential margins in 91% of cases in a cohort of 23 patients who underwent RAMPS. In a long-term follow-up data of the same series involving 47 patients after a median follow-up of 26 months, the median survival was 26 months and 5-year overall actuarial survival was 35.5%. In this cohort, the mean tumor size was 4.4 cm and R0 resection rate was 81% [2]. In the current series, the degree of differentiation has been observed to be an important predictor of poor prognosis with 3-year OS of 75% in well-differentiated tumors and 0% survival in poorly differentiated tumors. In another series involving 88 patients from Japan, the median survival was 22 months with a 5-year survival of 19%. However, well-differentiated cancers formed a significant proportion in this cohort and also lymph node involvement was demonstrated to be an independent predictor of long-term poor survival [12]. The outcomes of the most recent series for resections of distal pancreatic cancers have been shown in Table 3 and the results of our series reflect essentially similar results despite a larger tumor size and poor degree of differentiation.

In the current series, the perineural invasion, poor differentiation, and R+ resection have been shown to be significant risk factors for disease recurrence (Figs. 1 and 2). Among the multivariate analyses, margin status (R0 vs R1) remains the most important prognostic factor determining survival ($p = 0.023$). In the current series, the 3-year OS has been 64% for R0 resections compared with 25% for R1 resections. This finding advocates the necessity for radical surgical approaches in order to procure survival benefit in these aggressive cancers. In the current series, this procedure has shown improved survival even for pathologies other than pancreatic adenocarcinoma since preoperative histologic diagnosis was not routinely indicated in patients with distal pancreatic tumors [25, 26]. Hence, the modular approach should be considered routinely for all tumors involving the body and tail of the pancreas and not just pancreatic cancer. Furthermore, these tumors have a better tumor biology compared with pancreatic cancer and this procedure may actually further help improve their long-term outcomes.

In a recent series from Japan, 53 patients who had undergone RAMPS have been compared with 40 patients who underwent standard retrograde pancreatosplenectomy. RAMPS procedure resulted in better lymph node yield (28.4 ± 11.6 vs 20.7 ± 10.1; $p = 0.001$), more frequent R0 resection

Table 2 Prognostic factors for survival in pancreatic cancer by univariate analysis ($n = 27$)

S.No.	Prognostic factor	3-year overall survival	p value	3-year disease-free survival	p value
1.	Margins				0.014
	R0	64%	0.109	48%	
	R1	25%		0%	
2.	Lymphovascular invasion				0.420
	Present	38%	0.907	0%	
	Absent	50%		31%	
3.	Perineural invasion				0.048
	Present	26%	0.133	0%	
	Absent	78%		58%	
4.	Adjuvant chemotherapy				0.370
	Yes	49%	0.651	0%	
	No	60%		60%	
5.	Tumor differentiation				0.019
	WD	75%	0.056	75%	
	MD	47%		0%	
	PD	0%		0%	
6.	T stage				0.881
	T1	100%	0.651	0%	
	T2	56%		49%	
	T3	42%		21%	
	T4	0%		0%	
7.	Nodal metastases				0.319
	Present	0%	0.264	0%	
	Absent	63%		40%	
8.	Multivisceral resection				0.285
	Performed	34%	0.339	21%	
	Not indicated	65%		45%	
9.	CA-199 > 1000 U/L				0.123
	Yes	43%	0.306	0%	
	No	53%		35%	

p values which are significant have been italicized to attract reader's attention.

(90.5 vs 67.5%; $p = 0.005$), and better median survival. R1 resection, histologic grade, and vascular invasion were found to be independent risk factors for overall survival [27].

The concept of nodal dissection in RAMPS procedure has been extensively studied based on the anatomic models of lymphatic drainage of the pancreas [3]. In the study done by O'Morchoe et al., the nodes which are considered N1 or regional were primarily divided into two groups. The first ring of nodes was identified to encompass the gastrosplenic nodes seen in gastrosplenic omentum, splenic hilar nodes, infrapancreatic nodes, and gastroduodenal nodes. The second group were identified around the celiac and superior mesenteric arteries where there can be direct drainage of the pancreas to these nodal stations. Thus, for a satisfactory clearance, all these nodes need to be resected including the celiac nodes and nodes around the superior mesenteric artery. However, Fujita et al. have shown that lymph nodes attached to the pancreas were the most frequent metastatic nodes and they significantly affect the survival. In their study, most of the nodal involvement was seen in the superior and inferior borders of the pancreas and only rarely nodal metastases were seen in the celiac nodes and splenic hilum [17]. However, in the current series, the nodal involvement was seen only in 7 patients (26%) compared with other series with more than 50% nodal positivity [14]. A plausible explanation to the low nodal yield in this series can be an evolving pattern for diligent grossing and benchside dissections that happens in the histopathology unit and similar trends have been observed in pancreaticoduodenectomy as well [28]. Reiterating the importance of nodal prognostic factor, the current series shows 3-year OS of 63% for node-negative patients compared with 0% for nodal positive patients.

The role of adjuvant chemotherapy following pancreatic cancer resection has been extensively investigated in many large randomized trials. In the recent ESPAC 4 randomized trial comparing adjuvant gemcitabine plus capecitabine versus gemcitabine alone in resected pancreatic cancers, the median

Table 3 Resected cancers of distal body and tail of pancreas—recent series with outcomes

Author	Year	Country	No. of patients	Margins R0%	Mean tumor size cm	Operative mortality %	Median survival months	5-year survival %
Shimada [12]	2006	Japan	88	75	NS	0	22	19
Christein [13]	2005	USA	66	78	5.5	0	16	10
Kooby [14]	2010	USA	212	74	4.4	1.1	16	19
Kanda [15]	2010	Japan	51	74	NS	0	13	6
Yamamoto [16]	2010	Japan	73	76	3.3	0	NS	30
Fujita [17]	2010	Japan	50	90	4.0	0	23	19
Wu [18]	2010	China	45	NS	4.7	2	15	0
Kang [19]	2010	Korea	45	87	4.2	0	28	29
Rosso [20]	2013	France	52	90	4.65	0	20.5	3-year 20.7
Kitagawa [21]	2014	Japan	24	88	3.5	0	NS	53
Trottman [22]	2014	USA	26	88	NS	NS	NS	NS
Murakawa [23]	2015	Japan	49	83.7	NS	0	22.6	3-year 38.6
Grossman [24]	2016	USA	78	85	4.7	0	25	25

OS was 28 months in combination group versus 25.5 months in single agent group ($p = 0.032$) [29]. In the distal pancreatic cancers, Yamamoto et al. have documented a 5-year survival rate of 51% following gemcitabine administration in a cohort of 73 patients [16]. The tolerance depends on the performance status of these patients after a radical surgery as some large series have reported in the range of 34 to 68% patients completing adjuvant therapy with variations across the globe [2, 14, 16]. In these aggressive distal cancers, where the only hope of cure lies in the radical surgery with negative margins,

Fig. 1 Survival curve showing DFS for distal pancreatic cancers stratified according to the R0/R1 status ($n = 27$)
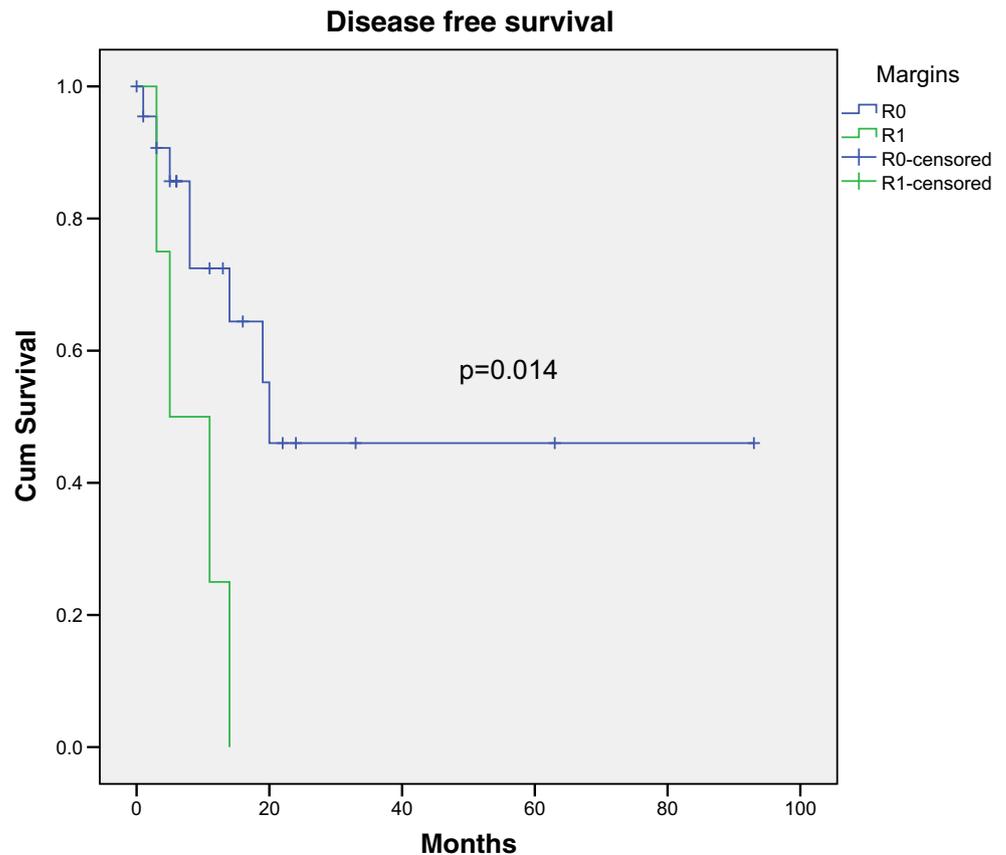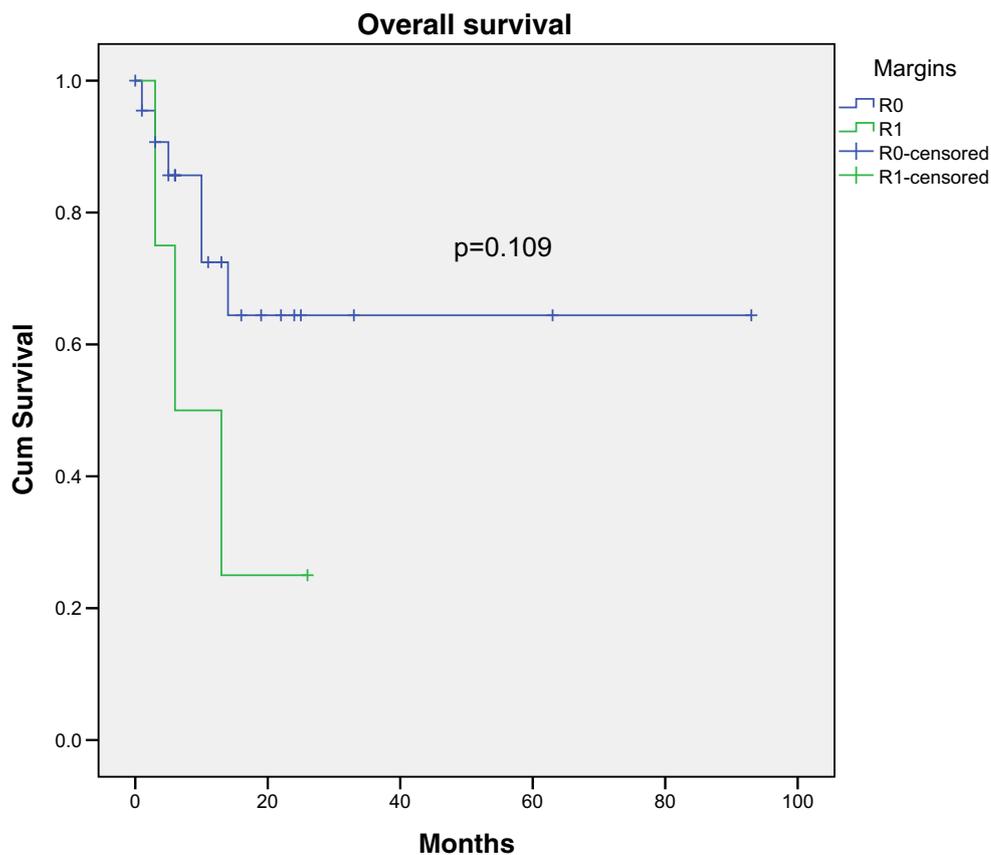
Fig. 2 Survival curve showing OS for distal pancreatic cancers stratified according to the R0/R1 status ($n = 27$)

Conclusion

RAMPS procedure has evolved as a paradigm shift in the surgical management of cancers of the body and tail of the pancreas. It aids in achieving high negative tangential resection margins and improved survival not only in pancreatic adenocarcinoma but also for other pathologies. Since preoperative histologic diagnosis is not routinely indicated for distal tumors and tumors other than pancreatic cancer carry a much better prognosis, RAMPS should be considered as the standard for all operable tumors involving body and tail of the pancreas irrespective of underlying histology.

adjuvant chemotherapy does have a role to make a difference in survival especially when concomitant poor prognostic factors exist such as nodal positivity, poor differentiation, perineural invasion, and margin positivity.

There have been many studies where the feasibility of laparoscopic approaches for distal pancreatic tumors has been discussed. In a Spanish report, 18 patients underwent laparoscopic distal pancreatosplenectomy with a median tumor size of 7 cm. The R1 resections have been high at a rate of 50% although the morbidity rates have been at acceptable range. However, the series emphasizes the feasibility of the laparoscopic approach even for larger tumors [30]. In a multicentric American series involving 212 patients who underwent distal pancreatosplenectomy, 23 patients have underwent laparoscopically. In a matched analysis, Kooby et al. have shown that the rates of positive margins, number of nodes harvested, and overall survival have not differed between open and laparoscopic approaches and also potential shorter hospital stay in laparoscopic surgery [14]. In yet another Korean series, 12 patients have underwent laparoscopic RAMPS and on comparing with the open group using the propensity score analysis, there was no difference in median overall survival [31]. In the current series, five patients have underwent laparoscopic RAMPS and one patient by robotic approach demonstrating the feasibility of the minimally invasive approach in selected distal pancreatic tumors.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval The data of the present study were collected in the course of common clinical practice and accordingly, the signed informed consent was obtained from each patient for any clinical procedure as well as for clinical data procurement. The study protocol was in accordance with ethical standards of the institutional research committee and the 1964 Helsinki Declaration and its later amendments. Since this was a retrospective study, formal consent for this study is not required and no approval of the institutional research committee was needed.

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