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REVIEW ARTICLE

High-risk lesions in the remnant pancreas: fate of the remnant pancreas after pancreatic resection for pancreatic cancer and intraductal papillary mucinous neoplasms

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Abstract
Progress in diagnostic modalities, surgical procedures, and multidisciplinary treatment for pancreatic diseases has increased the number of long-term survivors after pancreatic resection. Several reports have focused on high-risk lesions (HRLs), including high-grade pancreatic intraepithelial neoplasia (PanIN), pancreatic ductal adenocarcinoma, high-grade intraductal papillary mucinous neoplasm (IPMN), and IPMN with an associated invasive carcinoma, in the remnant pancreas after partial pancreatic resection for pancreatic cancer or IPMN. The etiology of HRLs in the remnant pancreas is thought to be either isolated local recurrence of the initial lesion in the remnant pancreas or a newly developed primary lesion. Although it is difficult to distinguish between local recurrence and a new primary lesion, comparison of genetic alterations between two lesions may help with this distinction. Early detection of HRLs in the remnant pancreas may improve the prognosis of patients, and several investigators have proposed predictive factors for HRLs in the remnant pancreas after partial pancreatic resection for pancreatic cancer or IPMN. The reported short- and long-term outcomes of surgical resection of HRLs in the remnant pancreas are relatively favorable. Life-long surveillance of the remnant pancreas is recommended after partial pancreatic resection for pancreatic cancer or IPMN.

Keywords Remnant pancreas · Pancreatic cancer · Intraductal papillary mucinous neoplasm

Introduction

Since the first distal pancreatectomy was performed by Trendelenburg in 1882 and the first pancreaticoduodenectomy was performed by Codivilla in 1898 [1], pancreatic resection has gradually become accepted as a treatment option for pancreatic diseases. Progress in operative procedures and devices, as well as perioperative management, has resulted in decreased postoperative mortality after pancreatic resection. Partial pancreatic resection is preferred to total pancreatectomy for preservation of exocrine and endocrine pancreatic function; however, the remnant pancreas after partial pancreatic resection may harbor metachronous lesions.

Pancreatic cancer is the most common indication for pancreatic resection [2, 3]. Although it is the most lethal gastrointestinal malignancy, early detection, facilitated by progress in diagnostic modalities and multidisciplinary treatment, has improved the prognosis of patients undergoing surgery for pancreatic cancer [4, 5]. Consequently, the number of long-term survivors after pancreatic resection for pancreatic cancer has been rising. Metachronous cancer develops in the remnant pancreas of some of these patients.

Intraductal papillary mucinous neoplasm (IPMN) has been widely accepted as a precursor lesion of pancreatic cancer and is occasionally subject to surgical resection. The prognosis after pancreatic resection for IPMN is favorable if it is resected before it has progressed to invasive cancer. IPMN is characterized by synchronous and metachronous multiple lesions and an association with distinct pancreatic ductal adenocarcinoma (PDAC) [6, 7]. Therefore, these

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lesions may develop in the remnant pancreas after partial pancreatic resection for IPMN.

High-grade pancreatic intraepithelial neoplasia (PanIN) and high-grade IPMN are noninvasive pancreatic ductal lesions with high-grade dysplasia, designated as "carcinoma in situ." Surgical resection is recommended for these lesions according to a revised classification system, and for precursor lesions in the pancreas [8]. Therefore, careful attention should be paid to the development of these noninvasive lesions as well as invasive lesions, including PDAC and IPMN, with associated invasive carcinoma in the remnant pancreas. The term "malignant" was used historically to indicate such noninvasive and invasive lesions. However, this use of the term "malignant" should be avoided, especially for IPMN [8, 9]. Several authors have designated these noninvasive and invasive pancreatic ductal lesions as "high-risk lesions" (HRLs) [10–12]. In this article, we adopt the term "HRLs" to describe pancreatic ductal lesions comprehensively, including high-grade PanIN, PDAC, high-grade IPMN, and IPMN with an associated invasive carcinoma. The early detection of HRLs in the remnant pancreas during postoperative surveillance may enable curative treatment with a better prognosis for patients who have undergone partial pancreatic resection for pancreatic cancer or IPMN.

In this article, we review the developmental mechanisms, predictive factors, and treatments of HRLs in the remnant pancreas after partial pancreatic resection for pancreatic cancer and IPMN.

HRLs in the remnant pancreas after pancreatic resection for pancreatic cancer

During the last two decades, several authors have reported cases of resection of HRL from the remnant pancreas after partial pancreatic resection for pancreatic cancer (Table 1) [13–25]. Interestingly, 10 of the 15 cases summarized in Table 1 were reported from Japan [13, 15, 18–25]. The surgical margins at the initial surgery were negative in all 15 cases and the median interval between the initial and secondary operations was 48 months (range 12–94 months). The histopathological diagnosis of the initial and secondary tumors was mixed acinar–ductal carcinoma in one case [22] and adenocarcinoma in all the others.

Recent cohort studies focusing on HRLs in the remnant pancreas after pancreatic resection for pancreatic cancer have also been reported (Table 2) [10, 26–37]. According to these studies, HRLs developed in the remnant pancreas of 0.7–26.7% of the patients who underwent pancreatic resection for pancreatic cancer. Two studies of early-stage pancreatic cancer showed higher incidences of HRLs in the remnant pancreas (26.7% and 15.5%) [27, 29], while the others showed incidences of HRL in the remnant pancreas of < 6%. The median interval between the initial resection and the diagnosis of HRLs in the remnant pancreas ranged from 2 to 6 years, and the longest interval was 240 months. The median resection rate of HRLs in the remnant pancreas was 78.5% (range 52.1–100%).

Table 1 Case reports of resected high-risk lesions in the remnant pancreas after partial pancreatic resection for pancreatic cancer

Authors	Year	Age (years)	Sex	Initial surgery	Surgical margin at the initial surgery	Interval (months)	Second surgery	Prognosis after second surgery
Eriguchi et al. [15]	2000	67	F	DP	Negative	88	TRP	8 months alive
Wada et al. [25]	2001	52	F	PD	Negative	22	TRP + Sp + DG	NA
Takamatsu et al. [24]	2005	63	M	PD	Negative	43	TRP + Sp	10 months alive
Dalla Valle et al. [14]	2006	63	M	PD	Negative	12	TRP + Sp + DG	24 months alive
Tajima et al. [23]	2008	58	M	PD	Negative	36	TRP + Sp	38 months alive
Koizumi et al. [20]	2010	65	M	PD	Negative	85	TRP + Sp	10 months alive
Koizumi et al. [20]	2010	67	M	DP	Negative	28	TRP	8 months alive
Ogino et al. [21]	2010	63	F	PD	Negative	70	TRP + Sp	13 months alive
Ogino et al. [21]	2010	56	M	PD	Negative	35	TRP + Sp	7 months alive
Ikematsu et al. [18]	2011	59	M	DP	Negative	65	TRP + PV	14 months alive
Kinoshita et al. [19]	2011	67	M	PD	Negative	68	TRP + Sp	2 months alive
Shonaka et al. [22]	2014	71	F	DP	Negative	15	TRP	21 months alive
Akabori et al. [13]	2014	52	F	DP	Negative	94	TRP	20 months alive
Hamner et al. [17]	2015	73	F	PD	Negative	48	TRP + Sp	11 months alive
Frei et al. [16]	2017	70	F	PD	Negative	74	TRP	21 months alive

F female, *M* male, *PD* pancreaticoduodenectomy including pylorus-preserving pancreaticoduodenectomy, *DP* distal pancreatectomy, *TRP* total remnant pancreatectomy, *Sp* splenectomy, *DG* distal gastrectomy, *PV* resection of portal vein, *NA* not available

Table 2 Cohort studies of HRLs in the remnant pancreas after partial pancreatic resection for pancreatic cancer

Authors	Year	Patients who underwent pancreatectomy for PDAC	HRLs in the remnant pancreas	Initial operation	R0/R1	Interval between the initial operation and HRLs in the remnant pancreas (months)	Resected HRLs in the remnant pancreas
Thomas et al. [36]	2012	700	5	NA	NA	Median 68 (range 7–81)	5
Hashimoto et al. [26]	2014	227	9	PD 6, DP 3	8/1	Median 24 (range 17–86)	7
Miyazaki et al. [32]	2014	284	11	PD 7, DP 4	9/2	Median 32 (range 7–89)	11
Shima et al. [34]	2015	185	6	PD 4, DP 2	6/0	Median 25 (range 12–60)	6
Ishida et al. [28]	2016	130	6	PD 3, DP 3	5/0	Median 43.5 (range 14–60)	4
Suzuki et al. [35]	2016	826	23	PD 12, DP 11	20/3	Median 53.6 (range 15–240)	12
Ikemoto et al. [27]	2018	30	8	PD 3, DP 6	NA	Median 56.5 (range 16–76)	5
Kanno et al. [29]	2018	200	31	NA	NA	NA	NA
Luchini et al. [30]	2018	NA	6	PD 5, DP 1	4/2	Median 37 (range 16–50)	6
Matsuda et al. [31]	2018	379	14	PD 4, DP 10	12/2	Median 42.5 (range 20–160)	10
Nakayama et al. [33]	2018	194	11	PD 8, DP 3	11/0	Median 24 (range 6–41)	11
Yamada et al. [37]	2018	NA	114	PD 66, DP 47, MP 1	102/11	Mean 38.6 ± 24.2 (resected cases), mean 42.8 ± 39.2 (unresected cases)	90
Gotoh et al. [10]	2019	411	22	NA	NA	NA	12

PDAC pancreatic ductal adenocarcinoma, *HRLs* high-risk lesions, *PD* pancreaticoduodenectomy including pylorus-preserving pancreaticoduodenectomy and duodenum-preserving pancreatic head resection, *DP* distal pancreatectomy, *MP* middle pancreatectomy, *NA* not available

Various terms have been used to describe HRLs, especially PDAC, in the remnant pancreas after pancreatic resection for pancreatic cancer. These terms include "recurrence in the remnant pancreas" [14, 27, 32, 33], "recurrent pancreatic cancer in the remnant pancreas" [34, 37], "cancer arising in the remnant pancreas" [30], "carcinoma developing in the remnant pancreas" [13, 16, 23], "second primary pancreatic ductal carcinoma" [28], "metachronous pancreatic cancer" [17], "remnant pancreatic cancer" [35], and "cancer in the remnant pancreas" [26, 31].

Developmental mechanisms of HRLs in the remnant pancreas after pancreatic resection for pancreatic cancer

Two possible mechanisms underlie the development of HRLs in the remnant pancreas after resection of pancreatic cancer: local recurrence of the initial pancreatic cancer; and the metachronous occurrence of a new primary lesion. The authors of some of the abovementioned case reports assumed that the secondary lesions were recurrences because of the histopathological similarity of the initial and secondary lesions and the short interval between the initial operation and detection of the secondary lesions, even though the surgical margins from the initial operation were negative [14, 25]. Other authors considered that the secondary lesions were new primary lesions because of the long interval between the initial operation and detection of the secondary lesions [13, 16, 18, 23]. However, many authors also reported that it was difficult to distinguish between local recurrence and a new primary lesion.

Because of the aggressive nature of pancreatic cancer, recurrence develops in approximately 80% of patients who undergo resection of pancreatic cancer [38–40]. Local recurrence is one of the most common patterns of recurrence of pancreatic cancer. Other patterns include liver metastasis and peritoneal dissemination with occasional development in the remnant pancreas [38–41]. Although local recurrence is often associated with distant metastasis, isolated local recurrence is recognized in 17–33% of patients with recurrence

after pancreatic cancer resection [32, 38–40]. Cancer cells of the initial lesion reach the remnant pancreas through several possible pathways, such as a positive surgical margin, hematogenous metastasis, lymphogenous spread, and intraductal dissemination [25, 30]. Recurrence through the latter three pathways is possible even when the initial and secondary lesions are apart from each other.

Several studies have suggested that patients with pancreatic cancer often have multifocal HRLs within the pancreas. Histopathological analyses of the pancreas after total pancreatectomy for PDAC showed that 20–32% of cases had multifocal disease [42, 43]. Histological comparison of the pancreas between patients with familial pancreatic cancer and sporadic pancreatic cancer showed that 65% of the patients with familial pancreatic cancer and 35% of the patients with sporadic pancreatic cancer harbored at least one PanIN 3 (corresponding to high-grade PanIN) [44]. Metachronous occurrence of new primary lesions in the remnant pancreas may be due to metachronous development of multifocal HRLs or enlargement of HRLs that were not detectable at the time of the initial surgery. Gotoh et al. [10] classified HRLs in the remnant pancreas into recurrence and multifocal lesions according to mutational and immunohistochemical analyses and suggested that there was a shorter interval between the initial and secondary lesions, a shorter distance from the initial pancreatic cut margin and secondary lesion, and a greater cumulative recurrence rate than in multifocal lesions.

Although it is difficult to distinguish between local recurrence and a new primary lesion in the remnant pancreas, even after resection of the secondary lesion, several investigators have attempted to separate local recurrence from a new primary lesion. Hashimoto et al. [26] used a pyrosequencing assay for KRAS mutation and immunohistochemistry for MUC1 and MUC2. Luchini et al. [30] compared histopathological features and KRAS mutation patterns assessed by next-generation sequencing between the primary and secondary lesions. Gotoh et al. [10] evaluated "founder mutation" in PDAC by mutational analysis of KRAS and immunohistochemical analyses of TP53, CDKN2A, and SMAD4. While resection of new primary lesions resulted in favorable long-term outcomes, the prognosis of patients who had undergone resection for local recurrence was similar to that of patients with unresectable secondary HRLs or extrapancreatic recurrence [10]. Distinction between local recurrence and a new primary lesion at the time of diagnosis of the secondary lesion may allow for the determination of an appropriate treatment strategy.

Predictive factors for HRLs in the remnant pancreas after pancreatic resection for pancreatic cancer

Identifying factors predictive of the development of HRLs in the remnant pancreas would help to establish a postoperative surveillance schedule after resection for pancreatic cancer. Matsuda et al. [31] analyzed 379 cases of resected PDAC and found that metachronous HRLs developed in the remnant pancreas in 14. They identified concomitant IPMN as an independent predictive factor for HRLs in the remnant pancreas among 15 clinicopathological features at the time of the initial pancreatic resection [31]. They also found that PDAC concomitant with IPMN had more PanIN lesions, including high-grade PanIN, in the background pancreas than PDAC without IPMN. This concomitant IPMN may reflect cancer susceptibility of the entire pancreas harboring it.

HRLs in the remnant pancreas after pancreatic resection for IPMN

Because IPMN is characterized by multifocal lesions, several studies have focused on the development of lesions in the remnant pancreas after pancreatic resection for IPMN (Table 3) [11, 12, 45–56]. These studies documented the development of HRLs in the remnant pancreas of 1.5–6.7% of patients who underwent pancreatic resection for IPMN. Six of the 14 studies listed in Table 3 included only patients with noninvasive IPMN at the initial surgery, suggesting that even patients with noninvasive IPMN require postoperative surveillance to detect HRLs in the remnant pancreas. Several studies reported > 10-year intervals between the initial pancreatic resection and the development of HRLs in the remnant pancreas [11, 12, 47, 52, 56]. The median resection rate of HRLs in the remnant pancreas was 60.8% (range 0–100%). These HRLs included both PDAC and IPMN because a pancreas harboring IPMN is at a high risk of the development of PDAC distinct from IPMN [57–59].

"Recurrence" has been used frequently to describe lesions that have newly developed or enlarged in the remnant pancreas after pancreatic resection for IPMN [47–50, 54–56, 60, 61]. Some authors have used "new lesion" [51, 52] or "progression" [12, 45, 53] to describe these lesions. "Recurrence," "new lesion," and "progression" in the remnant pancreas include not only HRLs, but also radiologically detected cysts that do not require surgical intervention. "Recurrence" also indicates extrapancreatic local recurrence or distant metastasis. It may be necessary to standardize the terminology of lesions in the remnant pancreas after pancreatic resection for IPMN according to the necessity of treatment.

Developmental mechanisms of HRLs in the remnant pancreas after pancreatic resection for IPMN

Pea et al. [12] proposed three patterns of developmental mechanisms of neoplastic lesions in the remnant pancreas after pancreatic resection for IPMN. The first pattern is residual

Table 3 Cohort studies of HRLs in the remnant pancreas after partial pancreatic resection for IPMN

Authors	Year	Patients who underwent pancreatectomy for IPMN	Patients who underwent pancreatectomy for noninvasive IPMN	Follow-up period[a]	Development or progression of remnant pancreatic lesion	HRLs in the remnant pancreas	Resected HRLs in the remnant pancreas
White et al. [55]	2007	78	78	Median 40 months	6	5	2
Schnelldorfer et al. [54]	2008	208	145	Mean 3.2 years	11	3	0
Fujii et al. [47]	2010	104	104	Mean 47.0 months	9	7	5
Miller et al. [51]	2011	191	191	Mean 66 months	31 (+38)[b]	6	3
Moriya and Traverso [52]	2012	203	160	Median 40 months	17 (+14)[b]	3	2
He et al. [48]	2013	130	130	Median 38 months	22	8	6
Marchegiani et al. [50]	2015	173	106	Median 56 months	14	5	5
Yogi et al. [56]	2015	153	118	Median 46.4 months	NA	10	6
Hirono et al. [49]	2016	257	172	Median 53.5 months	14	13	7
Miyasaka et al. [11]	2016	195	160	Median 47 months	29	13	10
Rezaee et al. [53]	2016	374	277	Median 28 months	62	13	8
Blackham et al. [46]	2017	100	100	Median 35 months	9	4	2
Pea et al. [12]	2017	260	260	NA	50	16	9
Al Efishat et al. [45]	2018	319	299	Median 42 months	71	15	8

IPMN intraductal papillary mucinous neoplasm, *HRLs* high-risk lesions, *NA* not available

[a]Follow-up period of all patients who underwent pancreatectomy for IPMN. [b]Residual lesions

microscopic disease at the surgical margin recurring in the remnant pancreas; namely, recurrence after R1 resection. In this pattern, the initial and secondary lesions are close to the surgical margin and genetically related. The second pattern is intraductal spread of neoplastic cells. In this pattern, the initial and secondary lesions are physiologically separated but genetically related. Date et al. [62] examined main duct-type IPMN in 12 patients with synchronous or metachronous separated lesions and reported that separated lesions were monoclonal in 8, suggesting that some of the multiple lesions in main duct type IPMN might be caused by intraductal dissemination from one lesion. The third pattern is multifocal disease, in which the initial and secondary lesions are both primary and genetically unrelated. In one study, 25–41% of branch duct type IPMN was multifocal [63]. An assessment of clonality of multifocal IPMN revealed that genetic alterations of separated lesions were independent in 69% of the patients [64].

Guideline-recommended surveillance for HRLs in the remnant pancreas after pancreatic resection for IPMN

Several groups have proposed guidelines for the management of IPMN [63, 65, 66]. All recommend postoperative surveillance after resection for IPMN to detect the development of remnant pancreatic lesions if patients are fit for surgery. Although the American Gastroenterological Association guideline restricts this surveillance to only patients after pancreatic resection for HRLs and does not recommend routine postoperative surveillance for patients after pancreatic resection for low-grade IPMN [66], international consensus guidelines and European guidelines recommend life-long surveillance for all patients after pancreatic resection for IPMN [63, 65].

Predictive factors for HRLs in the remnant pancreas after pancreatic resection for IPMN

The predictive factors for the development of lesions in the remnant pancreas have been investigated in several studies. Some examined factors correlated with recurrence, including both extrapancreatic lesions and remnant pancreatic lesions [50, 56, 61]. Others focused on remnant pancreatic lesions. He et al. [48] reported that a family history of pancreatic cancer was an independent predictive factor for a new lesion in the remnant pancreas after resection of noninvasive IPMN. Frankel et al. [60] concluded that the location within the body and dysplasia at the margin after pancreatic resection for noninvasive IPMN were independent predictors of recurrence in the remnant gland. Al Efishat et al. [45] retrospectively examined 319 patients with noninvasive and microinvasive IPMN ($\leq$ 10-mm invasive component) and found that distal lesions were associated with progression in the multivariate analysis. Hirono et al. [49] reviewed 257 cases of IPMN resection and found that a positive margin after pancreatic resection was an independent predictive factor for recurrence in the remnant pancreas. However, these four studies included radiologically detected cysts that required no intervention. Rezaee et al. [53] identified IPMN with high-grade dysplasia (high-grade IPMN) as an independent predictor of development of PDAC after resection of noninvasive IPMN. We separated HRLs into high-grade/invasive IPMN and PDAC and analyzed the predictive factors of each [11]. According to our results, the predictive factors for high-grade/invasive IPMN in the remnant pancreas were initial pathologic results of high-grade/invasive IPMN and IPMN located in the distal pancreas, and those for PDAC in the remnant pancreas were a pancreato-biliary subtype and the presence of concomitant PDAC at the time of the initial operation.

Treatment for HRLs in the remnant pancreas

HRLs in the remnant pancreas are treated by surgical resection, chemotherapy, and radiotherapy, as for initial HRLs. Although some HRLs may be recurrent disease and surgery could be difficult because of adhesion and changes in the anatomy, surgical resection is often performed for lesions restricted to the remnant pancreas. Chemotherapy or chemoradiotherapy is given for locally advanced disease, HRLs with distant metastasis, or patients who refuse reoperation [35, 45, 49, 67]. Ishida et al. [28] reported the case of a patient who had been treated by carbon ion radiotherapy and survived for 45 months without disease progression.

The most common surgical procedure for HRLs in the remnant pancreas is total remnant pancreatectomy [68], but partial pancreatectomy is performed in some cases [11, 26, 32, 34]. The postoperative morbidity rate after surgical resection for HRLs in the remnant pancreas ranges from 0.0 to 41.6% [32, 34, 35, 37]. Hashimoto et al. [69] reported that the morbidity rate after total remnant pancreatectomy was comparable to that after one-stage total pancreatectomy. They also reported that total remnant pancreatectomy after distal pancreatectomy was a more complicated procedure than total remnant pancreatectomy after pancreaticoduodenectomy [69]. No postoperative mortality was reported. Laparoscopic surgery has been performed increasingly for pancreatic disease, as well as other digestive diseases [70]. Some reports have described laparoscopic total remnant pancreatectomy after pancreaticoduodenectomy [71, 72].

Several authors have reported that the prognosis of patients who undergo resection of HRLs in the remnant pancreas is better than that of those treated nonsurgically [31–33, 35, 37]. Zhou et al. [73] performed a pooled analysis of 19 studies on second pancreatectomy for PDAC in the remnant pancreas and reported that the 5-year overall survival rate after second pancreatectomy was 40.6%. This may be higher than that of patients who undergo initial pancreatic resection for PDAC. Adjuvant chemotherapy after pancreatic resection reportedly improved the prognosis of patients with resectable pancreatic cancer [74, 75]. Nakayama et al. [33] reported that patients who received adjuvant therapy after total remnant pancreatectomy for PDAC in the remnant pancreas had a significantly better prognosis than those who did not. In contrast, the pooled analysis by Zhou et al. [73] revealed no significant correlation between adjuvant therapy and survival.

Conclusion

The "take-home message" of this review is summarized in Table 4. The number of patients found to have HRLs in the remnant pancreas after pancreatic resection is expected to increase. To date, postoperative surveillance after pancreatic resection for pancreatic cancer or IPMN has focused on recurrence of the initial disease. Although recurrence of the initial lesion usually develops within 5 years after surgery, HRLs can develop a long time after surgery. Surgeons should pay attention to this pathology, and the lifelong surveillance of patients who undergo partial pancreatic resection for pancreatic cancer or IPMN may be necessary.

Table 4 Take home massage

The remnant pancreas after partial pancreatic resection for pancreatic cancer or IPMN has a relatively high possibility of developing HRLs
The etiology of HRLs in the remnant pancreas is either recurrence of the initial lesion or a new primary lesion
HRLs in the remnant pancreas may occur even after a long period of time has passed since the initial operation
The prognosis of patients who undergo surgery for HRLs in the remnant pancreas is relatively favorable

HRLs high-risk lesions

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in association with this manuscript.

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