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Prediction of tumor recurrence after surgical resection of ampullary adenocarcinoma using magnetic resonance imaging

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Abstract

Objectives To predict tumor recurrence in patients who underwent surgical resection of ampullary adenocarcinoma using preoperative magnetic resonance (MR) imaging findings combined with clinical findings.

Methods In this multicenter study, a total of 113 patients (mean age, 62.9 ± 9.8 years; 58 men and 55 women) with ampullary adenocarcinoma who underwent preoperative MR imaging and surgery with margin-negative resection between 2006 and 2017 were retrospectively included. The MR imaging findings were evaluated by two radiologists. Preoperative clinical findings were obtained. Cox proportional regression analyses were used to identify the independent prognostic factors for recurrence-free survival (RFS). A nomogram was created based on the multivariable analysis and was internally validated.

Results Multivariable analysis revealed that presence of infiltrative tumor margin (hazard ratio [HR]: 2.18, $p = 0.019$), adjacent organ invasion (HR: 3.31, $p = 0.006$), adjacent vessel invasion (HR: 5.42, $p = 0.041$), peripancreatic lymph node enlargement (HR: 2.1, $p = 0.019$), and jaundice (HR: 1.93, $p = 0.043$) were significantly associated with worse RFS of ampullary adenocarcinoma after surgical resection. These MR imaging and clinical findings were used to construct a nomogram. On internal validation, the calibration plots showed excellent agreement between the predicted probabilities and the actual rates of tumor recurrence, with Harrell's c-index of 0.746.

Conclusions Combination of preoperative MR imaging and clinical findings can be useful for predicting tumor recurrence after surgical resection of ampullary adenocarcinoma. Identifying these features before surgery may aid in better treatment planning and management of these patients.

Clinical relevance statement A predictive nomogram using preoperative MR imaging and clinical findings can be useful in estimating the recurrence-free survival after surgical resection of ampullary adenocarcinoma.

Key Points

- *Presently, tumor size on imaging is the only non-invasive factor that correlates with recurrence-free survival from ampullary adenocarcinoma; other factors are obtained postoperatively.*
- *Infiltrative tumor margin, adjacent organ invasion, adjacent vessel invasion, peripancreatic lymph node enlargement on MRI, and jaundice are significant predictors for recurrence.*

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• *A nomogram incorporating significant MR imaging and clinical findings showed good performance in predicting recurrence-free survival, which can help in treatment planning.*

Keywords Ampulla of Vater, Carcinoma, Magnetic resonance imaging, Prognosis

Introduction

Ampullary adenocarcinoma is a relatively rare malignancy, representing less than 1% of all gastrointestinal cancers and 6% of periampullary cancers [1]. Compared to other malignant tumors in the periampullary region, carcinoma in the ampulla of Vater has a higher rate of resection [2]. According to previous reports, the recurrence rate after surgical resection of the tumor in the periampullary area is 34.4–42.5% for ampulla of Vater cancers [3, 4], 39–67% for distal common bile duct cancers [5, 6], and 80–90% for pancreatic cancers [7]. The favorable prognosis of ampullary carcinomas is due to the relatively early manifestation of obstructive symptoms compared with other periampullary tumors, owing to the small and complex structure of the ampulla of Vater [8].

Surgical resection of the tumor is the best chance for curative treatment of ampullary adenocarcinoma [9, 10]. Previous studies have demonstrated that early disease stage, negative lymph nodes, negative resection margins, and lower differentiation grade are related to better prognosis [10–12]. However, all these findings can only be assessed after surgical resection of the tumor. Evaluating each patient's prognostic factors prior to surgery may minimize the risk of unnecessary surgical complications and may identify those who could benefit from additional treatment.

Yoen et al [13] reported that, among various contrast-enhanced computed tomography (CT) and clinical findings of ampullary adenocarcinoma patients, tumor size on CT was the only significant variable after multivariable analysis for prediction of disease-free survival. Although CT is widely used for the initial evaluation of patients with ampullary adenocarcinoma due to its good spatial resolution and easier accessibility, magnetic resonance (MR) imaging may be superior for more precise evaluation of the ampullary tumor and its surrounding structures due to the better soft-tissue resolution. However, to our knowledge, no study has yet been published to evaluate the preoperative MR imaging and clinical findings useful in predicting tumor recurrence in patients with surgically resected ampullary adenocarcinoma.

Thus, the purpose of this study was to evaluate the value of preoperative MR imaging and clinical findings for predicting the recurrence-free survival (RFS) in patients with ampullary adenocarcinoma after surgical resection and to combine those findings to construct a predictive nomogram.

Materials and methods

This retrospective study was conducted at three tertiary medical centers (Severance Hospital, Soonchunhyang University Bucheon Hospital, and Inha University Hospital, in the Republic of Korea). The institutional review board for each center approved this study and waived the requirement to obtain written informed consent.

Study population

We searched the electronic databases of the three institutions and collected data from 568 patients with pathologically proven ampullary adenocarcinoma with surgical resection of the tumor between January 2006 and December 2017. Among these patients, 455 were excluded due to following criteria: (1) positive resection margin on the surgical pathologic report ($n = 28$); (2) no preoperative MR examination ($n = 173$); 3) inadequate preoperative MR imaging quality for analysis ($n = 4$); (4) biliary intervention prior to MR examination ($n = 233$); and 5) preoperative MR examinations performed more than 3 months prior to surgery ($n = 17$). Finally, a total of 113 patients with surgically resected ampullary adenocarcinoma were included in the analysis. The flowchart of the study population is shown in Fig. 1.

MR examination

All MR examinations were performed using one of these 1.5-T or 3-T MR imaging systems: Magnetom Avanto, or Magnetom Skyra (Siemens Healthineers), Intera Achieva (Philips Healthcare), and Discovery MR 750w, or Signa HDxt (GE Healthcare). The MR imaging included single-shot or multishot T2-weighted imaging, T1-weighted dual gradient-echo imaging (in- and opposed-phase), T1-weighted three-dimensional gradient-echo imaging with dynamic contrast-enhancement, and diffusion-weighted imaging (DWI). The T1-weighted sequences were obtained before and after intravenous injection of gadoterate meglumine (Dotarem; Guerbet) or gadobutrol (Gadovist; Bayer Healthcare) at a rate of 2.0 mL/s (0.1 mmol per kilogram of body weight), or gadoxetate disodium (Primovist, Bayer Healthcare) at a rate of 1.0 mL/s (0.025 mmol per kilogram of body weight). A test-bolus or bolus-tracking method was used for initiation of arterial phase scanning, and portal venous phase (60 s), and delayed phase (3 min) images were obtained. Further details of the MR imaging sequences are listed in Table S1.

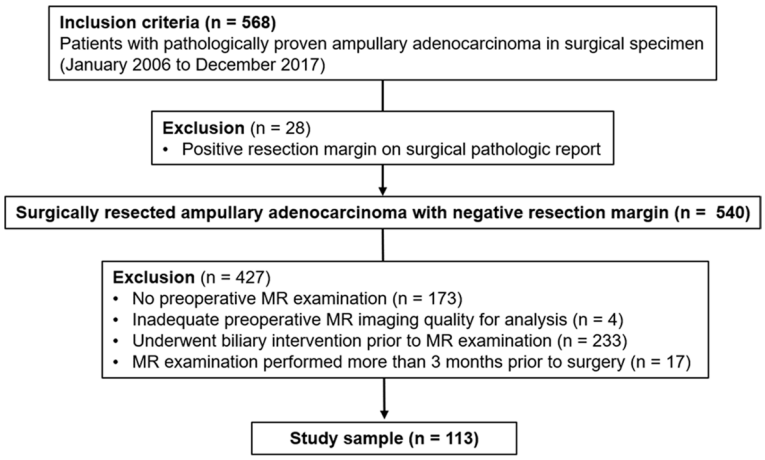

Fig. 1 Flow chart of the study population

The mean interval between the MR examination and surgery was 21.7 ± 15.0 days (range, 3–85 days). In this study, we included all preoperative pancreatobiliary MR examinations with or without contrast-enhancement or DWI; 95 patients (84.1%) with contrast-enhanced MR imaging with DWI, 10 patients (8.8%) with contrast-enhanced MR imaging without DWI, and eight patients (7.1%) with MR imaging without DWI.

Clinical data collection

We gathered clinical patient data from electronic medical records, including demographic characteristics, preoperative levels of serum total bilirubin, and serum carbohydrate antigen 19-9 (CA 19-9). The patient was classified as having jaundice if his/her serum total bilirubin levels were above 2.5 mg/dL. A serum CA 19-9 level above the normal limit of 37 U/mL was considered elevated. These laboratory test results were obtained within three weeks of the MR examination, prior to any biliary intervention. The pathology reports of patients' surgical specimens were reviewed. Although the most recent tumor staging follows the AJCC 8th edition, our study data was collected over an extended period of time in multiple centers, and used the AJCC 7th edition for data organization. After surgery, patients were scheduled for regular check-ups at the outpatient department every three to six months. These visits included imaging studies and serum tumor marker evaluations. The detection of local tumor recurrence or distant metastasis was based on follow-up reports from CT, MR imaging, positron emission tomography-CT scans, or pathology.

MR image analysis

Two board-certified gastrointestinal radiologists (S.L. and J.E.L., both with 12 years of experience in abdominal MR imaging) independently reviewed the imaging data using a picture archiving and communication system. Readers were blinded to the clinical outcome of the patients and after independent interpretation of the images, discrepancies between the readers were resolved by a consensus discussion including a third reader (S.C. with 15 years of experience in abdominal MR imaging).

For analysis, the following imaging findings were evaluated: ampullary mass size (mm); longest diameter in axial or coronal plane; presence of bulging ampulla, defined as distal common bile duct (CBD) lumen protruding into the duodenal lumen, beyond the original line of the choledochoduodenal junction [14]; mural shape (intramural or extramural, protruding); whether the epicenter of the tumor is exceeding the contour of the ampulla [13]; tumor margin (well-defined, infiltrative); pattern of distal CBD narrowing (normal, gradual tapering, or abrupt narrowing) [15]; diameter of CBD (mm); presence of adjacent organ invasion, defined as contiguous soft tissue lesions extending from the main tumor closely abutting or infiltrating into the adjacent organs, specifically duodenum and/or pancreas [16]; presence of adjacent vessel invasion, defined as caliber change or irregularity of the vessels with contiguity to the tumor (Fig. 2) [16]; main pancreatic duct (MPD) diameter (mm); presence of peripancreatic lymph node enlargement (short diameter > 1 cm) [17]; presence of diffusion restriction of the ampulla, defined as the ampullary mass having higher signal intensity on DWI (b = 800 s/mm^2) and lower signal intensity on apparent diffusion coefficient map compared to the adjacent normal duodenal wall [18]; and enhancement of the ampullary mass on arterial and portal venous phases (iso, hypo, or hyper signal intensity compared to the duodenal wall).

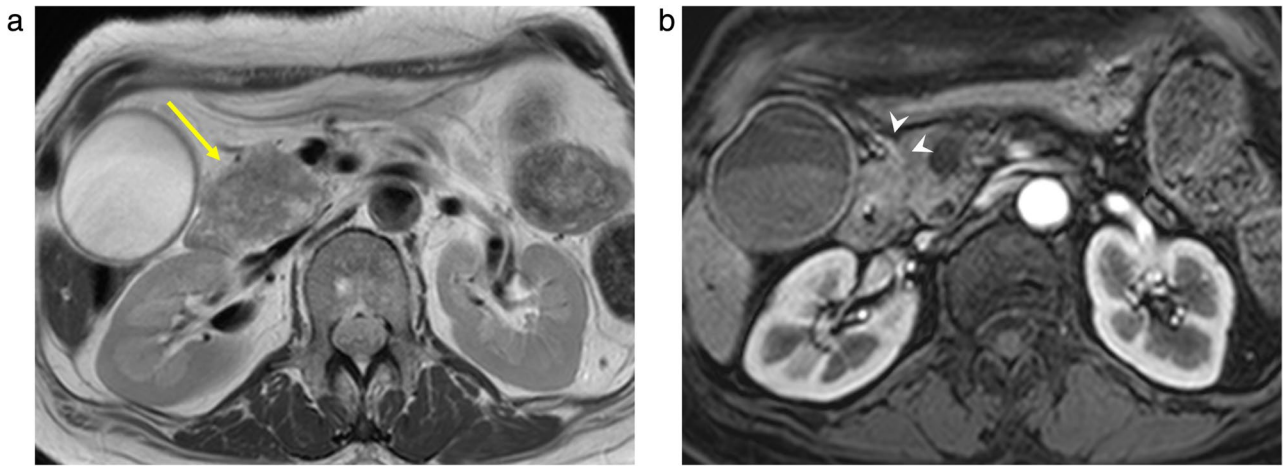

Fig. 2 Images of a 64-year-old female with ampullary adenocarcinoma, showing infiltrative tumor margin, adjacent organ, and vessel invasion. Axial T2-weighted magnetic resonance image (**a**) shows a 5.8 cm sized ampullary mass (yellow arrow) with infiltrative tumor margin and direct invasion of adjacent duodenum and pancreas. Arterial phase of the axial contrast-enhanced T1-weighted image (**b**) shows encasement and luminal irregularity of the gastroduodenal artery (white arrowheads) due to direct invasion by the ampullary adenocarcinoma

Statistical analysis

All statistical analyses were performed using R version 3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria) and Rex version 3.0.3 (RexSoft Inc., Seoul, Republic of Korea). Interobserver agreement between the two reviewers was evaluated using the *k* value and intraclass correlation coefficients. The interpretation was done as follows: poor agreement, < 0.20; fair, 0.21–0.40; moderate, 0.41–0.60; good, 0.61–0.80; and excellent, 0.81–1.00. Using the final data made in consensus by the three reviewers, Cox proportional regression analyses were used to determine which preoperative MR imaging or clinical findings correlated with the RFS of ampullary adenocarcinoma patients after surgical resection. Variables with p-value < 0.05 in univariable analysis were further evaluated using multivariable analysis. Finally, a nomogram for 1-, 3-, and 5-year RFS was established using the variables that remained as independent predictors. Harrell's c-index and calibration plots were used to assess the accuracy of the nomogram. For the c-index, c = 0.5 indicates random change, and c = 1.0 indicates perfect prediction accuracy. A c-index of 0.7 or higher indicates excellent consistency.

Results

Clinical and pathological data

Basic clinical and pathological characteristics of the patients are shown in Table 1. One hundred thirteen patients with ampullary adenocarcinoma were evaluated in our study with a mean age of 62.9 ± 9.8 years (range,

Table 1 Clinical and pathological characteristics of the study population

Characteristics	Number (n = 113)
Age (years)*	62.9 ± 9.8
Sex	
Male	58 (51.3)
Female	55 (48.7)
Jaundice	58 (51.3)
Serum total bilirubin (mg/dL)**	3.1 (0.7–7.1)
Elevated CA 19–9	57 (50.4)
Serum CA 19–9 (U/mL)**	27.9 (10.0–104.7)
Surgery	
Pylorus-preserving pancreaticoduodenectomy	102 (90.3)
Pancreaticoduodenectomy	10 (8.8)
Extended pancreatectomy	1 (0.9)
T staging	
1	22 (19.5)
2	46 (40.7)
3	36 (31.9)
4	9 (8.0)
LN metastasis	
Negative	72 (63.7)
Positive	40 (35.4)
N/A†	1 (0.9)

Data are numbers of lesions with percentages

CA 19-9 carbohydrate antigen 19-9

* Data are mean ± standard deviation

** Data are median and interquartile ranges

† N/A specific pathologic information was not mentioned in the surgical pathologic report

38–81 years). Among them, 58 (51.3%) were men and 55 (48.7%) were women. The median preoperative serum total bilirubin level was 3.1 mg/dL (interquartile range [IQR], 0.7–7.1 mg/dL), and 58 patients (51.3%) had jaundice. The median preoperative serum CA 19-9 level was 27.9 U/mL (IQR, 10.0–104.7 U/mL), and 57 patients (50.4%) had elevated serum CA 19-9 level. Patients underwent pylorus-preserving pancreaticoduodenectomy (n = 102, 90.3%), pancreaticoduodenectomy (n = 10, 8.8%), or extended pancreatectomy (n = 1, 0.9%).

In pathologic reports for surgical resection of ampullary adenocarcinoma, the most common T-stage was T2 (n = 46, 40.7%), followed by T3 (n = 36, 31.9%) and T1 (n = 22, 19.5%). As for lymph node metastasis, 40 patients (35.4%) had positive lymph node metastasis.

MR imaging features of ampullary adenocarcinoma

The mean size of the ampullary tumor was 25.0 ± 10.1 mm, with 54 (47.8%) lesions showing bulging ampulla. A majority of the tumors showed extramural, protruding type (n = 69, 61.1%), well-defined margin (n = 80, 70.8%), and abrupt narrowing of the distal CBD (n = 82, 72.6%). Sixty-one (54.0%) lesions showed adjacent organ invasion (only duodenal invasion, n = 61; duodenal and pancreas invasion, n = 21), and 29 (25.7%) had peripancreatic lymph node enlargement. Seventy-two (63.7%) lesions showed diffusion restriction of the tumor, and there was no dominant pattern regarding the enhancement of the tumor (Table 2).

Interobserver agreement

All qualitative imaging variables exhibited good or excellent interobserver agreement (k = 0.65–0.92), except mural shape (k = 0.58), tumor margin (k = 0.56), and enhancement pattern on portal venous phase (k = 0.60), which exhibited moderate interobserver agreement. All three quantitative imaging variables exhibited excellent interobserver agreement (k = 0.92–0.95) (Table S2).

Tumor recurrence and prognostic factors for RFS

After surgical resection of the tumor, 45 patients (39.8%) presented with tumor recurrence on follow-up studies, where 11 patients (24.4%, 11/45) had local tumor recurrence, 30 patients (66.7%, 30/45) had distant metastasis, and four patients (8.9%, 4/45) had both at the time tumor recurrence was detected. The detailed locations of metastasis for the 34 patients who developed distant metastasis were: distant lymph nodes (n = 9), liver (n = 12), lung (n = 2), peritoneal carcinomatosis (n = 4), and multiple sites (n = 7). The median RFS time was 49.4 (IQR, 16.2–74.1) months.

Table 2 Magnetic resonance imaging features of the study population

Magnetic resonance imaging features	Number (n = 113)
Ampullary mass size (mm)*	25.0 ± 10.1
Bulging ampulla	54 (47.8)
Mural shape	
Intramural	44 (38.9)
Extramural, protruding	69 (61.1)
Tumor margin	
Well-defined	80 (70.8)
Infiltrative	33 (29.2)
Pattern of distal CBD narrowing	
Normal	4 (3.5)
Gradual tapering	27 (23.9)
Abrupt narrowing	82 (72.6)
CBD diameter (mm)*	17.1 ± 5.2
Adjacent organ invasion	61 (54.0)
Adjacent vessel invasion	2 (1.8)
MPD diameter (mm)*	4.2 ± 2.7
Peripancreatic lymph node enlargement	29 (25.7)
DWI (b = 800 s/mm^2)	
Diffusion restriction of ampulla	72 (63.7)
N/A†	18 (15.9)
Enhancement pattern	
AP	
Iso	47 (41.6)
Hypo	18 (15.9)
Hyper	40 (35.4)
N/A†	8 (7.1)
PVP	
Iso	41 (36.3)
Hypo	20 (17.7)
Hyper	44 (38.9)
N/A†	8 (7.1)

Data are numbers of lesions with percentages

AP arterial phase, CBD common bile duct, *DWI* diffusion-weighted image, *MPD* main pancreatic duct, *N/A* not applicable, *PVP* portal venous phase

* Data are mean ± standard deviation

† N/A specific information was not obtained in the magnetic resonance examination

In the multivariable analysis, infiltrative tumor margin (hazard ratio [HR]: 2.18, 95% confidence interval [CI]: 1.14–4.16, p = 0.019), adjacent organ invasion (HR: 3.31, 95% CI: 1.42–7.75, p = 0.006), adjacent vessel invasion (HR: 5.42, 95% CI: 1.07–27.36, p = 0.041), peripancreatic lymph node enlargement (HR: 2.1, 95% CI: 1.13–3.92, p = 0.019), and presence of jaundice (HR: 1.93, 95% CI: 1.02–3.66, p = 0.043) were independent significant variables for worse RFS in patients with surgical resection of ampullary adenocarcinoma (Table 3).

Table 3 Magnetic resonance imaging and clinical characteristics for predicting recurrence-free survival after surgical resection of ampullary adenocarcinoma

Characteristics	Univariable			Multivariable		
	Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Magnetic resonance imaging variables						
Ampullary mass size (mm)	1.01	(0.98, 1.04)	0.404			
Bulging ampulla	0.81	(0.45, 1.46)	0.488			
Mural shape						
Intramural	…	…				
Extramural, protruding	0.59	(0.33, 1.07)	0.082			
Tumor margin						
Well-defined	…	…				
Infiltrative	3.8	(2.1, 6.86)	< 0.001	2.18	(1.14, 4.16)	0.019
Pattern of distal CBD narrowing						
Normal	…	…				
Gradual tapering	1.27	(0.16, 10.15)	0.823			
Abrupt narrowing	2.19	(0.3, 15.95)	0.441			
CBD diameter (mm)	1.04	(0.98, 1.09)	0.184			
Adjacent organ invasion	5.73	(2.66, 12.35)	< 0.001	3.31	(1.42, 7.75)	0.006
Adjacent vessel invasion	17.1	(3.52, 82.98)	< 0.001	5.42	(1.07, 27.36)	0.041
MPD diameter (mm)	1	(0.9, 1.12)	0.983			
Peripancreatic lymph node enlargement	2.97	(1.64, 5.4)	< 0.001	2.1	(1.13, 3.92)	0.019
DWI (b = 800 s/mm^2)* (n = 95)						
Diffusion restriction of ampulla	1.33	(0.58, 3.04)	0.497			
Enhancement pattern† (n = 105)						
AP						
Iso						
Hypo	2.11	(0.95, 4.7)	0.068			
Hyper	1.54	(0.77, 3.09)	0.223			
PVP						
Iso						
Hypo	2.2	(0.95, 5.11)	0.066			
Hyper	1.82	(0.89, 3.73)	0.1			
Clinical variables						
Age (years)	1.04	(1, 1.07)	0.037			
Sex	0.9	(0.5, 1.61)	0.712			
Jaundice	2.25	(1.21, 4.18)	0.011	1.93	(1.02, 3.66)	0.043
Elevated CA 19–9	1.1	(0.61, 1.97)	0.761			

AP arterial phase, *CA 19-9* carbohydrate antigen 19-9, *CBD* common bile duct, *DWI* diffusion-weighted image, *MPD* main pancreatic duct, *N/A* not applicable, *PVP* portal venous phase

* Data were calculated using only 95 cases with DWI

† Data were calculated using only 105 cases with dynamic contrast enhancement

Prognostic nomogram based on MR imaging and clinical findings

Using the significant MR imaging and clinical variables on multivariable analysis, we incorporated a prognostic nomogram to approximate the numerical probability of each patient's 1-, 3-, and 5-year RFS (Fig. 3) and obtained the calibration plots (Fig. 4). The points for each variable are on the uppermost scale marked as "points," representing the difference in the HRs. Thus, adjacent vessel invasion had the highest contribution to predicting the RFS of ampullary adenocarcinoma patients, followed by adjacent organ invasion, infiltrative tumor margin, peripancreatic lymph node enlargement, and jaundice. All points were summed to obtain the "total points," and a perpendicular line was drawn below to assess the recurrence-free probability in 1-, 3-, or 5-year after surgery

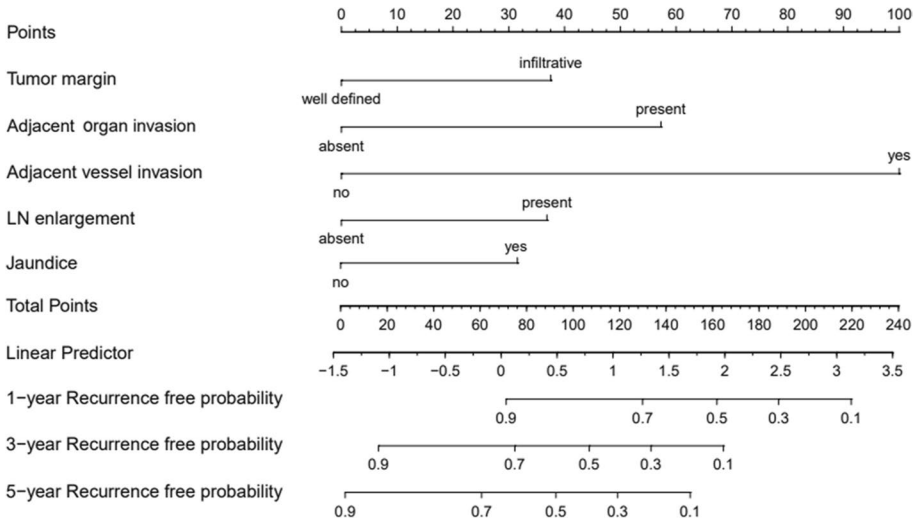

Fig. 3 A nomogram for predicting the recurrence-free survival after surgical resection of ampullary adenocarcinoma, based on magnetic resonance imaging and clinical findings. The points for each variable are found on the uppermost "points" scale. On the bottom scale, the points for all variables are added up into "total points" and translated into 1-, 3-, and 5-year recurrence-free probability

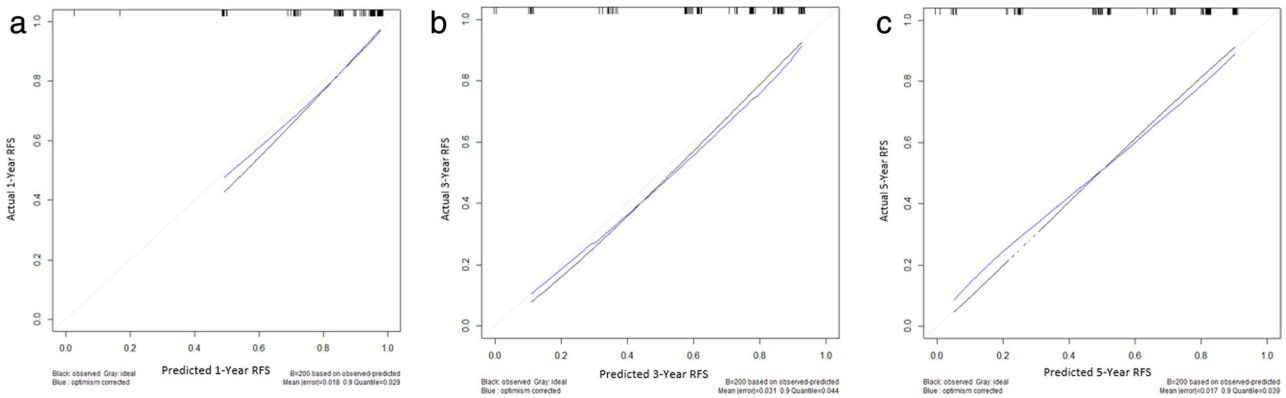

Fig. 4 Internal calibration plots for the nomogram were derived for predicting the 1-year (**a**), 3-year (**b**), and 5-year (**c**) recurrence-free survival after surgical resection of ampullary adenocarcinoma. In the calibration plots, the 45° gray line indicates the ideal nomogram, the black line indicates the apparent nomogram performance and the blue line indicates the nomogram performance calculated with bootstrap correction; the survival time plots exhibited good agreement.

(Figs. 5 and 6). The estimated Harrell's c-index was 0.746, which demonstrates excellent predictive accuracy and agreement between the predicted and observed values for the RFS.

Discussion

In our study, among various preoperative MR imaging and clinical findings, infiltrative tumor margin, adjacent organ invasion, adjacent vessel invasion, peripancreatic lymph node enlargement, and jaundice were independent significant variables for predicting the RFS in patients with ampullary adenocarcinoma. Among these findings, adjacent vessel invasion exhibited the highest HR. Additionally, we constructed a predictive nomogram for the estimation of patients' RFS, which showed excellent agreement between the predicted and actual probabilities on the calibration plot.

In previous studies [13, 19, 20], large tumor size was an important predictor of tumor recurrence after surgical resection of ampullary adenocarcinoma. It is apprehensible that a larger tumor size and greater tumor burden are likely to result in a poorer prognosis. However, in our study, the size of the ampullary mass was not a significant factor in predicting the RFS. Rather, infiltrative tumor margin remained as an independent significant variable even after the multivariable analysis. Since the ampulla

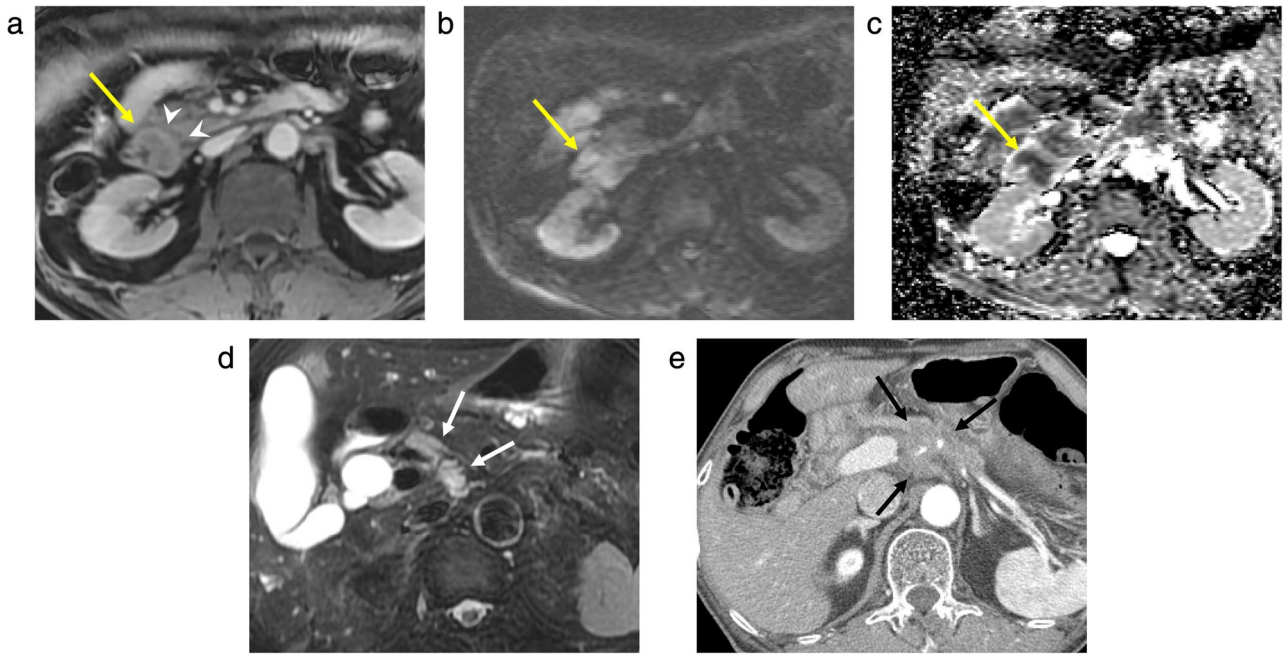

Fig. 5 Images of a 66-year-old male who presented with jaundice and was confirmed to have ampullary adenocarcinoma and had poor prognosis. Portal venous phase of axial contrast-enhanced T1-weighted magnetic resonance image (**a**) shows a 3.8 cm sized poorly enhancing ampullary mass (yellow arrow) with infiltrative tumor margin and direct invasion of adjacent duodenal wall and pancreatic head (white arrowheads). There was no evidence of adjacent vessel invasion. The mass (yellow arrows) shows diffusion restriction on axial diffusion-weighted imaging (*b* value, 800 s/mm^2) (**b**) and apparent diffusion coefficient map (**c**). Axial fat-suppressed T2-weighted image (**d**) shows enlarged lymph nodes (white arrows) in periportal areas. Based on the nomogram, his total points were 164, and the probability of 3-year recurrence-free survival was around 10%. On follow-up contrast-enhanced abdominal CT after 2.8 years (**e**), tumor recurrence (black arrows) was noted at the pancreato-jejunostomy site

of Vater is a complex structure composed of the distal CBD, pancreatic duct, and the duodenal papilla covered by the intestinal mucosa, ampullary adenocarcinoma can be subclassified into two types according to the tumor origin: intestinal type and pancreatobiliary type [1]. Previous studies by Ivanovic et al [21] and Chung et al [22] investigated the correlation of CT and MR imaging findings with histopathological subtypes. In both studies, pancreatobiliary subtypes more frequently showed infiltrative tumor margins compared to intestinal types, and the differences were statistically significant [21, 22]. Owing to the tumor origin, intestinal type tumors may easily grow into the duodenal lumen forming a nodular mass, while pancreatobiliary type develops along the biliary epithelium and may lead to a more infiltrative tumor morphology [21, 22]. A recent meta-analysis published by Zhou et al [23] reported that patients with pancreatobiliary-type tumors had worse overall survival and RFS compared with patients with intestinal-type tumors. Unfortunately, our study was unable to evaluate the impact of histopathological subtypes on RFS in ampullary adenocarcinoma patients. This limitation was due to the lack of specific data in most pathological reports and the multicentric nature of our study, which spanned over an extended period of time. Nonetheless, our findings align with the previous reports noting that the infiltrative tumor margin was a significant variable correlated with poorer RFS, which may potentially be attributed to the difference in histological subtypes.

Among the five independent significant variables for predicting the RFS in patients with ampullary adenocarcinoma, adjacent vessel invasion (HR: 5.42) showed the highest HR, followed by adjacent organ invasion (HR: 3.31). Our study results correlate well with the T staging guideline of the AJCC staging manual in which ampullary adenocarcinomas exhibiting more extensive invasion into adjacent organs or vascular structures are classified into higher T stages. Also, both variables showed good interobserver agreement, reflecting their usefulness in the preoperative evaluation of ampullary adenocarcinomas with MR imaging.

Numerous studies have repeatedly emphasized that lymph node metastasis is a well-established prognostic factor in ampullary adenocarcinoma patients who undergo curative resection [19, 24–26]. Lymph node involvement of the tumor may reflect the shift in the tumor behavior, transitioning from confinement at the primary tumor site toward distant metastasis, and

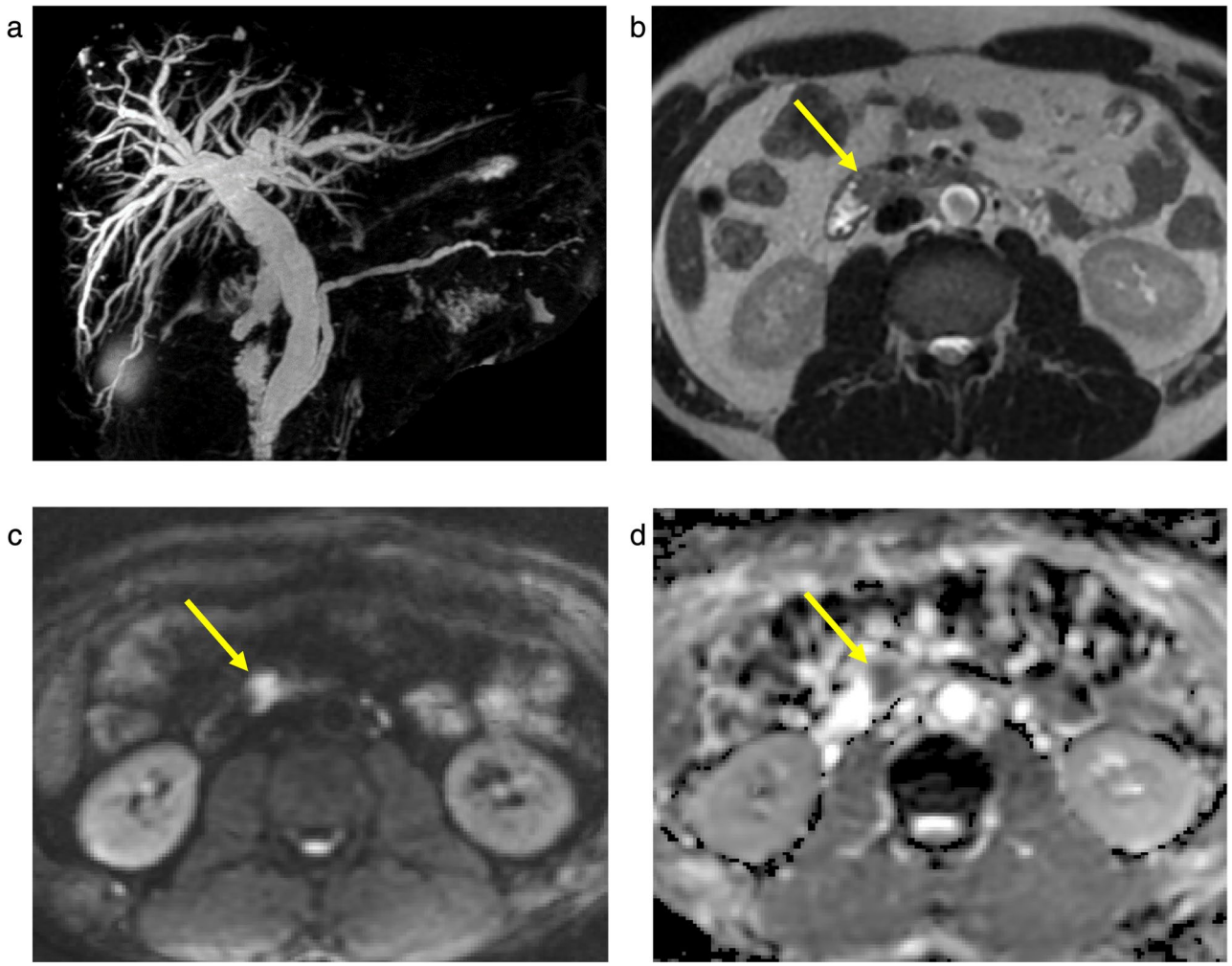

Fig. 6 Images of a 44-year-old male who presented with jaundice and was confirmed to have ampullary adenocarcinoma and had a good prognosis. Magnetic resonance cholangiopancreatography image **(a)** shows proportionate bile duct dilatation and diffuse main pancreatic duct dilatation up to the ampullary portion. Axial T2-weighted image (**b**) shows a 1.8 cm sized ampullary mass (yellow arrow) with a well-defined margin and no evidence of adjacent organ or vessel invasion. The mass (yellow arrows) shows diffusion restriction on axial diffusion-weighted imaging (*b* value, 800 s/mm^2) (**c**) and apparent diffusion coefficient map (**d**). There were no abnormal enlarged regional lymph nodes. Based on the nomogram, his total points were 32, and the probability of 5-year recurrence-free survival was around 80%. The patient lived to the end of the observation period with no evidence of tumor recurrence for more than eight years

dissemination of the tumor cells through the lymphatics likely contributes to poorer prognosis [26]. In contrast to previous studies [19, 24–26], which relied on post-surgical pathologic reports to assess the presence of tumor cells in the lymph nodes, our study results showed that preoperative evaluation of peripancreatic lymph node enlargement on MR imaging showed excellent interobserver agreement and was an independent variable that significantly correlated with RFS.

Among the clinical features, jaundice was the only independent significant variable for predicting RFS in ampullary adenocarcinoma patients. Yokoyama et al [27] reported that jaundice at presentation predicted an advanced stage of ampullary adenocarcinoma and poor prognosis. Another study by Kamisawa et al [28] reported that the cumulative 5-year and 10-year survival rates in jaundiced patients were worse than in anicteric patients with surgically resected ampullary adenocarcinoma. The results of our study align with the previous reports, indicating that patients who had jaundice at the time of diagnosis experienced worse RFS compared to those without.

The 5-year survival rate after curative resection of ampullary adenocarcinoma is reported to range from 30 to 68% [29, 30], which is relatively high compared to other periampullary cancers. However, recurrence is still a major cause of mortality in ampullary adenocarcinomas

and has a significant negative impact on survival outcomes. Our study's strength lies in the fact that compared to previous studies suggesting prognostic factors that can only be assessed after surgery, we demonstrated significant variables from preoperative evaluation for predicting RFS of patients with ampullary adenocarcinoma. Identifying these significant MR imaging and clinical variables prior to surgery can help physicians and surgeons better understand the tumor and improve clinical decision-making, such as considering neoadjuvant or adjuvant treatments. This proactive approach may contribute to a more tailored management strategy, ultimately improving outcomes for patients.

There are several limitations to our study. First, there is inevitable selection bias due to the retrospective design of our study. Second, despite the strength of a multicenter design, various types of MR vendors were used, and not all enrolled patients underwent contrast-enhanced MR imaging with DWI. Nevertheless, this variability is unlikely to affect our predictive nomogram significantly, as the enhancement pattern or diffusion restriction of ampullary adenocarcinoma did not exhibit statistical significance in the univariable analysis. Third, we had to exclude cases in which MR examination was conducted after biliary intervention due to the possible alterations of the signal intensity or findings in the periampullary area and the ampullary mass itself. Lastly, further validation through prospective studies with larger cohorts and external validation is needed to confirm the utility and reliability of our nomogram.

In conclusion, a nomogram constructed based on preoperative MR imaging and clinical findings can help prognosticate RFS in patients who undergo surgical resection of ampullary adenocarcinoma. In particular, the presence of infiltrative tumor margin, adjacent organ invasion, adjacent vessel invasion, peripancreatic lymph node enlargement, and jaundice were significant predictors of RFS, and identifying these features before surgery may aid in better management and treatment planning of these patients.

Abbreviations

CA 19-9	Carbohydrate antigen 19-9
CBD	Common bile duct
CI	Confidence interval
CT	Computed tomography
DWI	Diffusion-weighted imaging
HR	Hazard ratio
IQR	Interquartile range
MPD	Main pancreatic duct
MR	Magnetic resonance
RFS	Recurrence-free survival

Supplementary Information

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Below is the link to the electronic supplementary material. Supplementary file1 (PDF 154 KB)

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Declarations

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Conflict of interest
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Methodology

- Retrospective
- Observational study
- Multicenter study

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