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ORIGINAL ARTICLE

Underutilization of Surgery in Periampullary Cancer Treatment

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Abstract

Background Site-specific outcomes of resection for periampullary cancer have not been analyzed on a large, registry-based scale.
Methods We assessed data on periampullary cancers from the SEER database. Site- and stage-specific outcomes were analyzed. Resection was compared to no resection.
Results Resection was the main therapy in stages 1 and 2 (resection vs. no resection, 8644 vs. 7208 patients), was less frequent in stage 3 (1248 vs. 2783 patients) and was rarely—but still—used in stage 4 disease (541 vs. 11,212 patients). Pancreatic head (75.7%), 11.4% distal bile duct, 7.7% ampullary, and 5.3% duodenal cancers. Cancer subtype-independent median survival was 22.0 (resection) vs. 7.0 months (no resection) in stages 1 and 2, 21.0 vs. 8.0 months in stage 3, and 10.0 vs. 3.0 months in stage 4. Subtype-dependent median survival (resection vs. no resection) was 18.0 vs. 5.0 months in pancreatic head, 19.0 vs 4.0 months in distal bile duct, 41.0 vs 7.0 months in ampullary, and 38.0 vs 4.0 months in duodenal adenocarcinoma. On multivariable analysis, patient comorbidities, marital and insurance status, and income all influenced the decision to undergo resection.
Conclusions Surgery is still underutilized in the treatment of periampullary cancers. Patients with cancers originating from the duodenum or the ampulla of Vater benefit most from resectional surgery.

Keywords Periampullary cancer · Resection · SEER database

Introduction

Resection is a main-stay of treatment in periampullary cancers, comprising ampullary, duodenal, distal bile duct, and pancreatic head adenocarcinoma.[1–6] In general, resection is performed in stage 1 and 2 patients as the primary therapy, rarely in stage 3 patients, and is almost considered a contraindication in patients with stage 4 disease.[7,8] However, exceptions to this rule are made more and more often, either by not operating on stage 1 and 2 patients (frequently due to refusal of the patient or due to social reasons such as under-insurance) or by operating on stage 3 and 4 patients who had for a long time not been considered surgical candidates. An analysis utilizing the National Cancer Data Base (data from 1995 to 2004) describes that too few patients with pancreatic adenocarcinoma are operated on.[9] Colleagues from our university recently conducted a large-scale multicenter study on pancreatic cancer patients and demonstrated that resection was indeed associated with better survival.[10] However, none of these studies analyzed stage- or site-specific survival of periampullary cancers. We aimed at analyzing periampullary cancer outcomes on a registry-based level with a particular focus on a contemporary dataset.

Materials and Methods

All information was gathered from the SEER registry.[11] We obtained permission to access the research data files with the reference number "11928-Nov2013". Briefly, the SEER database has been established by the National Cancer Institute (NCI) and pools data from 18 population-based cancer

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registries, accounting for nearly 28% of the US population and recording almost 100% of cancer cases within each registry[12]; the SEER database has been widely used in studying outcomes in various malignancies.[13–17] This study did not include any interaction with human subjects or the use of personal identifying information.

Inclusion Criteria

The SEER*stat software (version 8.3.2 April 14, 2016) was used to identify patients with periampullary cancer. According to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3),[18] we selected patients with primary adenocarcinoma located at the extrahepatic bile duct (C24.0), the ampulla of Vater (C24.1), the duodenum (C17.0), or the head of the pancreas (25.0). Further inclusion criteria were as follows. Patients had to be 18 years or older, be diagnosed from January 1, 2004 to December 31, 2012, have microscopically confirmed disease, have active follow-up, have only one primary malignancy; in addition, for patients who underwent surgical resection, those with SEER surgery codes 10-27 (palliative interventions such as photodynamic therapy, electrocautery, fulguration, cryosurgery, laser) and 90 (surgery type unknown) were excluded. Patient entries lacking information on stage, resection, or survival time were excluded (in total, 4645 patients were excluded).

Variables

The following demographic and tumor variables from the SEER database were tabulated: age, sex, race, primary tumor site, stage, marital status, insurance, lymph node status, resection, and survival time. In addition, state, neoadjuvant radiotherapy, median family income per year, and comorbidity were compared in the surgery vs the non-surgery group. The American Joint Committee on Cancer (AJCC) 6th edition Cancer Staging system was used to identify patients with stage 1 and stage 2, stage 3, and stage 4 disease. Patients were followed up every month by the relevant registries or hospitals, and SEER upgraded the follow-up information annually.[19] For marital status, we defined single, divorced, separated, or widowed as single status. For the assessment of the lymph node status, we calculated the positive lymph node ratio (PLNR) using the equation: positive lymph node count divided by total lymph node count. The causes of the patients' death were extracted, as were long-existing chronic conditions such as cardiovascular and cerebrovascular disease and chronic infections.

Statistical Analysis

Continuous variables were compared using an independent sample *t* test. Categorical variables were analyzed using the chi-square test. Overall survival, defined as duration from the date of diagnosis to the date of death, was calculated using the Kaplan-Meier method. Differences between groups were assessed using the log-rank test. Survival time was censored if the patient was alive at the last follow-up. Cox proportional hazards models were used to adjust the survival analysis for potential confounders. Multivariate analysis was performed with a binary logistic regression model to identify factors predicting survival after resection or predicting no utilization of resection. A *P* value of less than 0.05 was considered statistically significant. All statistical analyses were carried out using IBM SPSS 22 (SPSS Statistics V22, IBM Corporation, Somers, New York).

Results

Patient Characteristics

A total of 31,636 patients diagnosed with periampullary cancer (PAC) between 2004 and 2012 were identified in the SEER database. Details of the patient characteristics are shown in Table 1. Most of the patients (50.1%) were registered as stage 1 or 2, followed by stage 4 (37.2%) and stage 3 (12.7%). The number of PAC cases increased with each year (data not shown).

Stage-Specific Survival, Resection Versus no Resection

In an initial analysis, we pooled patients from all subtypes of PAC and assessed outcomes depending on stages and whether resection had been performed or not. Median follow-up was 54 months. In stages 1 and 2, median survival was 22 versus 7 months (resection vs no resection, HR = 0.318, 95% confidence intervals (CIs) = 21.36–22.64 and 6.77–7.23, respectively; Fig. 1a), 21 vs 8 months in stage 3 (HR = 0.366, 95%-CIs = 19.44 to 22.57 and 7.62 to 8.38, respectively; Fig. 1b), and 10 vs 3 months in stage 4 (HR = 0.438, 95%-CIs = 8.70 to 11.30 and 2.89 to 3.11, respectively; Fig. 1c).

Tumor Subtype-Specific Survival, Resection Versus no Resection, all Stages

We then went on to analyze survival depending on the respective tumor subtype and resection vs no resection. Here, median survival for patients with pancreatic head cancers was 19 vs 7 months (stage 1/2; HR = 0.346, 95%-CI = 0.332–0.361, and $p < 0.001$; Fig. 2a), 14 vs 8 months (stage 3; HR = 0.592, 95%-CI = 0.517–0.677, and $p < 0.001$; Fig. 2b), and 9 vs 3 months (stage 4; HR = 0.482, 95%-CI = 0.429–0.542, and $p < 0.001$;Fig. 2c). And median survival for patients with distal bile duct cancer was 21 vs 6 months (stage 1/2; HR =

Table 1 Patient characteristics

Variable	Category	Number (%)
Age	Age ≤ 70	18,490 (58.4)
	Age > 70	13,146 (41.6)
Sex	Male	16,309 (51.6)
	Female	15,327 (48.4)
Race	Caucasian	25,146 (79.5)
	African American	3706 (11.7)
	AI/AN	189 (0.6)
	Asian/PI	2595 (8.2)
Primary Site	Pancreatic head	23,946 (75.7)
	Distal bile duct	3598 (11.4)
	Ampulla of Vater	2428 (7.7)
	Duodenum	1664 (5.3)
Stage	Stage 1/2	15,852 (50.1)
	Stage 3	4031 (12.7)
	Stage 4	11,753 (37.2)
Insurance	Uninsured	645 (2.0)
	Any Medicaid	1487 (4.7)
	Insured	18,379 (58.1)
	Medicare	7088 (22.4)
	Unknown	4037 (12.8)
Marital status	Single	12,613 (39.9)
	Married	18,019 (57.0)
	Unknown	1004 (3.2)
Surgery	No surgery	21,203 (67.0)
	Surgery performed	10,433 (33.0)

AI/AN American Indian/Alaska Native, *Asian/PI* Asian or Pacific Islander

0.342, 95%-CI = 0.308–0.380, and $p < 0.001$; Fig. 2d), 17 vs 8 months (stage 3; HR = 0.467, 95%-CI = 0.372–0.586, and $p < 0.001$; Fig. 2e), and 9 vs 3 months (stage 4; HR = 0.522, 95%-CI = 0.409–0.665, and $p < 0.001$; Fig. 2f). For patients with ampullary cancer, median survival was 55 vs 9 months (stage 1/2; HR = 0.232, 95%-CI = 0.199–0.270, and $p < 0.001$; Fig. 2g), 26 vs 7 months (stage 3; HR = 0.264, 95%-CI = 0.211–0.330, and $p < 0.001$; Fig. 2h), and 21 vs 5 months (stage 4; HR = 0.404, 95%-CI = 0.286–0.571, and $p < 0.001$; Fig. 2i). In addition, we also analyzed median survival for duodenal cancer patients; it was 67 vs 6 months (stage 1/2; HR = 0.276, 95%-CI = 0.221–0.345, and $p < 0.001$; Fig. 2j), 29 vs 9 months (stage 3; HR = 0.359, 95%-CI = 0.267–0.483, and $p < 0.001$; Fig. 2k), and 13 vs 4 months (stage 4; HR = 0.348, 95%-CI = 0.262–0.464, and $p < 0.001$; Fig. 2l).

Factors Associated with the Decision to Resect

In patients with stage 1 or 2 periampullary cancer, 8644 received a resection while 6495 were not recommended to undergo a resection (and accordingly did not receive surgery). According to the results of univariate and multivariate analysis (Table 2), age, tumor site, neoadjuvant radiotherapy, tumor size, marital status, insurance, median family income, and comorbidity were independent factors associated with the final decision to resect or to treat conservatively.

Although most of the patients with stage 4 periampullary cancer (10,689 patients) were not recommended to undergo surgery, 541 patients in this group received a resection. In these patients, being younger, a tumor located at the ampulla of Vater or in the duodenum, neoadjuvant radiotherapy, and a smaller tumor size were factors associated with the decision to proceed to surgery (Table 3).

Comparison of Survival in Resected Patients, Pancreatic Head Vs Other Cancers

To assess potential site-specific differences, we compared median survival of resected patients with pancreatic head cancer versus all other periampullary cancers (distal bile duct, ampullary, duodenal). Survival was stage-independently longer in the non-pancreatic head cancer group of patients (stage 1/2, 19 vs 36 months ($p < 0.001$; Fig. 3a); stage 3, 14 vs 24 months ($p < 0.001$; Fig. 3b); and stage 4, 9 vs 12 months ($p < 0.001$; Fig. 3c)).

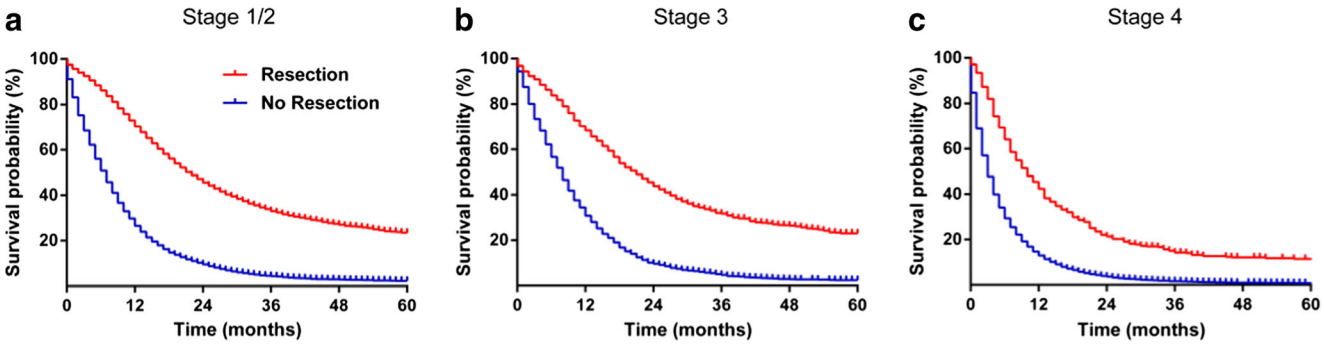

Fig. 1 Overall stage-specific survival. **a** Stage 1/2. **b** Stage 3. **c** Stage 4

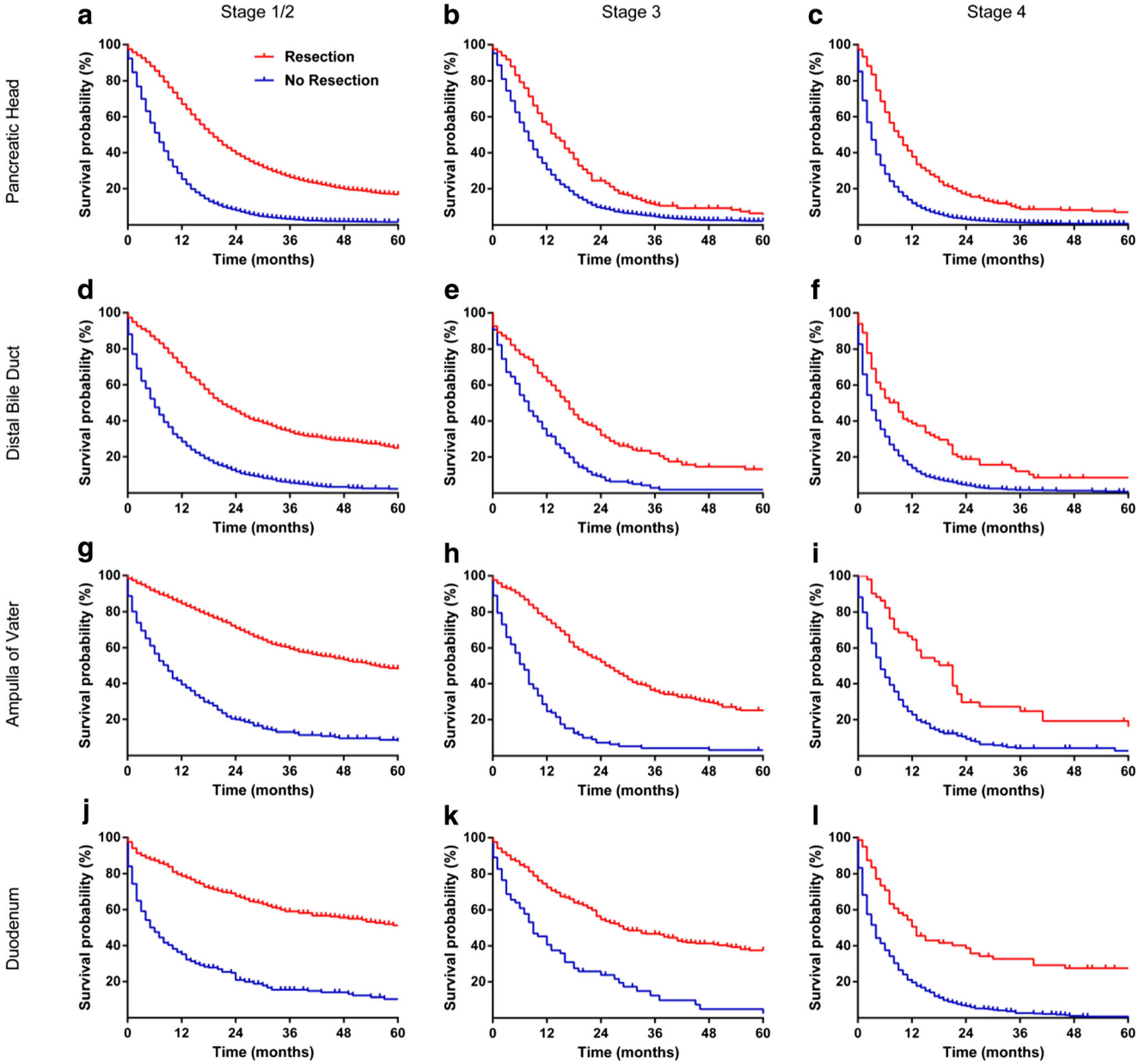

Fig. 2 Tumor subtype-specific survival. **a** Pancreatic head cancer, stage 1/2, **b** stage 3, **c** stage 4. **d** Distal bile duct cancer, stage 1/2, **e** stage 3, **f** stage 4. **g** Ampullary cancer, stage 1/2, **h** stage 3, **i** stage 4. **j** Duodenal cancer, stage 1/2, **k** stage 3, **l** stage 4

Factors Predictive of Survival in Patients Undergoing Resection

We then sought to determine factors predictive of survival in resected patients (Supplementary Tables 1 and 2). In univariate and multivariate analysis, none of the tested factors reached a hazard ratio of > 2. Due to the large number of patients, statistical significance was seen for almost all factors in univariate analysis and for a smaller number of factors in multivariate analysis. The strongest factor in multivariate analysis was a positive lymph node ratio of > 0.5, with a hazard ratio reaching 1.817.

Discussion

This large-scale analysis utilizing the SEER database assesses the impact of surgical resection on overall survival in periampullary cancers. In addition, factors associated with the decision to perform surgery are investigated. A number of novel findings are reported: First, resection was associated with a significantly better overall survival in all stages, most surprisingly also in the small subgroup of stage 4 patients. While these patients are usually not recommended to undergo resection, some single-center analyses have reported relatively good outcomes with such procedures.[20–22] To our knowledge,

Table 2 Factors associated with the decision of resection in patients with stage 1 or 2 periampullary cancer

Variable	Category	OR	95%CI	*P*
Age	Age ≤ 70	1		**< 0.001**
	Age > 70	0.531	0.473–0.597	
Race	Caucasian	1		0.170
	African American	0.836	0.694–1.006	0.058
	AI/AN	0.627	0.298–1.318	0.218
	Asian/PI	0.955	0.773–1.179	0.668
Sex	Male	1		0.318
	Female	0.943	0.841–1.058	
Site	Pancreatic head	1		**< 0.001**
	Distal bile duct	2.772	2.303–3.338	< 0.001
	Ampulla of Vater	7.889	6.173–10.083	< 0.001
	Duodenum	5.931	4.064–8.654	< 0.001
Radiation	None	1		**< 0.001**
	Before surgery	25.303	12.204–52.462	
Size	≤ 35 mm	1		**< 0.001**
	> 35 mm	0.576	0.511–0.649	
Marital status	Single	1		**< 0.001**
	Married	1.315	1.164–1.485	< 0.001
	Unknown	1.086	0.785–1.502	0.618
Insurance	Uninsured	1		**0.014**
	Any Medicaid	1.060	0.741–1.517	0.749
	Insured	1.328	0.954–1.848	0.092
	Medicare	0.744	0.643–0.897	0.003
Income	≤ 67,000 USD	1		**0.008**
	> 67,000 USD	1.165	1.041–1.304	
Comorbidity	None	1		**< 0.001**
	CCD	0.299	0.207–0.432	< 0.001
	Infection	0.326	0.165–0.645	0.001
	Other disease	0.289	0.143–0.584	0.001

Income means median family income per year.. Infection includes pneumonia and influenza, septicemia. Other disease contains diabetes mellitus, chronic liver disease and cirrhosis, chronic obstructive pulmonary disease, nephritis, nephrotic syndrome and nephrosis, stomach and duodenal ulcers. Bold values in the table represent significant values ($P < 0.05$). OR represents likelihood of resection. 1 means reference

CI confidence interval, *AI/AN* American Indian/Alaska Native; *Asian/PI* Asian or Pacific Islander, *CCD* cardiovascular and cerebrovascular disease

Table 3 Factors associated with the decision of resection in patients with stage 4 periampullary cancer

Variable	Category	OR	95%CI	*P*
Age	Age ≤ 70	1		**0.001**
	Age > 70	0.648	0.500–0.839	
Race	Caucasian	1		0.425
	African American	0.968	0.670–1.398	0.863
	AI/AN	0.000	0.000	0.997
	Asian/PI	1.369	0.938–1.997	0.103
Site	Pancreatic head	1		**< 0.001**
	Distal bile duct	4.470	3.090–6.465	< 0.001
	Ampulla of Vater	9.037	5.967–13.688	< 0.001
	Duodenum	9.833	6.798–14.233	< 0.001
Radiation	None	1		**< 0.001**
	Before surgery	18.472	6.667–51.182	
Size	≤ 35 mm	1		**0.001**
	> 35 mm	0.588	0.464–0.747	
Marital status	Single	1		0.115
	Married	1.302	1.014–1.672	0.039
	Unknown	1.093	0.540–2.211	0.806
Comorbidity	None	1		0.586
	CCD	0.587	0.258–1.334	0.688
	Infection	0.673	0.163–2.780	0.584
	Other disease	0.000	0.000	0.998

Income means median family income per year.. Infection includes pneumonia and influenza, septicemia. Other disease contains diabetes mellitus, chronic liver disease and cirrhosis, chronic obstructive pulmonary disease, nephritis, nephrotic syndrome and nephrosis, stomach and duodenal ulcers. Bold values in the table represent significant values ($P < 0.05$). OR represents likelihood of resection. 1 means reference

CI confidence interval, *AI/AN* American Indian/Alaska Native, *Asian/PI* Asian or Pacific Islander, *CCD* cardiovascular and cerebrovascular disease

no large-scale study showing this trend has been published so far.

Secondly, in our study, 6495 patients were not recommended to receive resection. This includes 41% of all the patients with stage 1 or 2 disease, which are per se promising candidates for a potentially curative resection. This phenomenon might partially be explained by patients being too old and/or too sick for major abdominal surgery. Albeit we could not get information about comorbidity directly from the SEER database, we hypothesized that the cause of death recorded in SEER could be a surrogate for comorbidities. This approach illustrates one of the limitations of large-scale retrospective analyses and shows that further prospective studies in the field are urgently needed. From the extrapolated factors, larger tumor size and older age were negative indicators for resection, while a tumor located at the ampulla of Vater or in the duodenum and neoadjuvant radiotherapy were positive factors for resection. In patients with stage 1 or 2 cancer, lower family income, Medicare insurance, being single, and the existence of comorbidities were negative factors for resection. These findings could indicate that, next to old age and comorbidities, social status is also associated with the rate of resection. Furthermore, social factors including marital status can correlate to deficits in treatment and outcome in a variety of diseases as well.[23,24]

Third, looking at stage 4 patients, tumors located at the ampulla of Vater or in the duodenum were associated with a better prognosis compared to the other entities and were

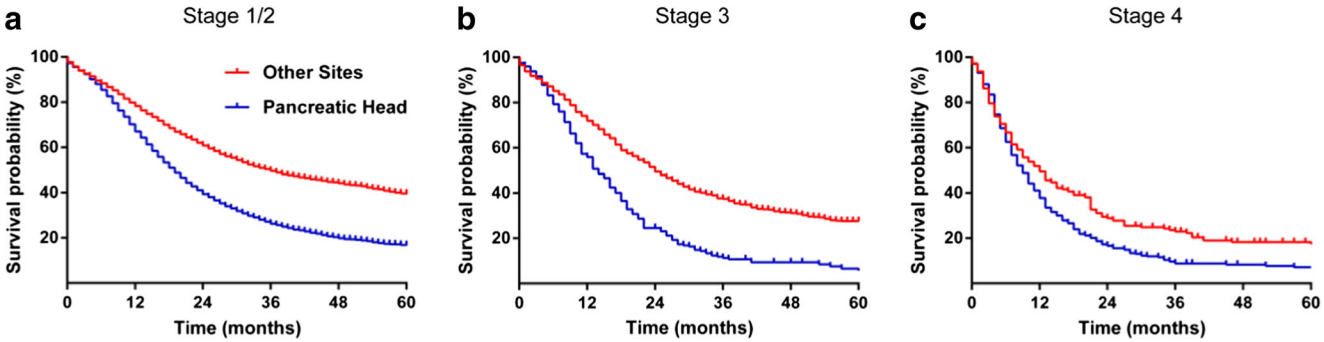

Fig. 3 Survival in resected patients, pancreatic head vs other cancers. **a** Stage 1/2. **b** Stage 3. **c** Stage 4

operated on more often. This points towards a significantly different tumor biology compared to pancreatic ductal adenocarcinoma and distal bile duct cancer. In line with such an assumption, there is supposed to be a small group of stage 4 patients who might benefit from surgery. This underlines the importance of correct preoperative assessment of the tissue of origin.

Next, according to our results from univariate and multivariate analysis, a positive lymph node ratio is a crucial prognostic factor in patients undergoing resection, which is recapitulated in a large number of recent papers.[25–31] While highly specific recommendations for the resection of lymph nodes exist for a variety of gastrointestinal malignancies, such a system is lacking for periampullary carcinomas. Development of a multi-tier N-staging system with meaningful cut-off values, adjusted to the tissue of origin, is a priority in periampullary cancer research.

However, our study has several limitations: While the SEER database represents one of the powerful tools in epidemiological studies, it certainly does lack some information. Crucial factors that are not presented here include comorbidities (as discussed above), precise information on chemotherapy, other medication, and other possible reasons that could have led to not receiving a resection, even when indicated (e.g., personal preference, religious believe). One additional source of bias is of course the retrospective nature of this study and the underlying dataset. These limitations indicate that the findings presented in this study need to be verified in prospective multicenter studies.

The data presented in this study was collected from 2004 to 2012. The most recent trends and developments in the field were not reflected in this dataset. In comparison to the study by Bilimoria et al. that assessed data collected from 1995 to 2004, the rate of resection went up from 28.6% in their study (stage 1 pancreatic cancer) to 51.6% in the current study (stage 1 or 2 pancreatic head cancer). Although different databases have been utilized and the comparability of the studies is not too high, there is still some progress in utilization of surgery during the last decade, which could be attributed to improved surgical techniques and peri-operative management, resulting in lower morbidity and mortality rates and thus in a wider acceptance of complex pancreatic resectional surgery.

Conclusion

This study suggests that resection of pancreatic cancer is still underutilized but that some progress has been made lately. Secondly, resection of periampullary cancers could increase overall survival, even in subsets of patients with locally advanced disease. The different tumor sites should be taken into account before surgery, as patients with cancers originating from the duodenum and the Ampulla of Vater might benefit most from a resection. Thirdly, factors leading to exclusion of a certain patient subset from a potentially beneficial surgical resection need to be further assessed and if possible adjusted.

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Authors' Contribution Christoph W. Michalski, Bing Liu, and Max Heckler designed the study, performed data acquisition and statistical analysis, and prepared the manuscript.

Susanne Roth, Ulrike Heger, and Huihui Sun contributed to the quality control of the data and to manuscript editing.

Markus W. Büchler and Thilo Hackert contributed to the design of the study and edited the manuscript.

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