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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Does the Extent of Resection Impact Survival for Duodenal Adenocarcinoma? Analysis of 1,611 Cases

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ABSTRACT

Background. Because duodenal adenocarcinoma (DA) is relatively rare, few studies have investigated the impact of resection type on long-term outcomes.

Methods. The Surveillance, Epidemiology, and End Results database was used to identify all patients between 1988 and 2010 with DA. Patients were divided into two groups based on the type of surgery received: simple resection (SR), defined as a simple removal of the primary site, and radical resection (RR), defined as removal of the primary site with a resection in continuity with other organs. Differences in disease-specific survival (DSS) and overall survival (OS) were compared.

Results. Of the 1,611 patients included, 746 (46.3 %) underwent SR and 865 (53.7 %) underwent RR. As expected, patients undergoing RR were more likely to present with poorly differentiated and large tumors, as well as advanced stage disease. Despite greater lymph node (LN) retrieval (11.0 vs. 6.8; $p < 0.0001$), RR was not associated with improved survival (5-year DSS and OS rates of 52.8 and 41.3 % for SR vs. 48.8 and 37.6 % for RR; $p > 0.05$). On univariate Cox proportional hazards regression analysis, the type of surgery was not associated with OS (odds ratio [OR] 0.98; 95 % confidence interval [CI] 0.87–1.11). Increasing TNM stages, tumor grade, fewer LNs removed, LN ratio, and absence of radiation were associated with worse survival. After controlling for confounding factors, type of surgery still did not influence OS (OR 1.11; 95 % CI 0.97–1.27).

Conclusions. Radical resection (e.g., in the form of pancreaticoduodenectomy) does not appear to impact survival compared with simple segmental resection for DA.

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Although the duodenum is the most common site for adenocarcinoma of the small intestine, duodenal adenocarcinoma (DA) remains a rare malignancy, comprising <1 % of all gastrointestinal cancers.[1,2] Because of its rarity, there is a scarcity of well-designed studies to guide management. In general, DA has a more favorable outcome compared to other periampullary malignancies (pancreatic adenocarcinoma, ampullary adenocarcinomas, and distal cholangiocarcinomas) and therefore, aggressive surgical resection has been recommended. However, the extent of resection required for DA has long been the subject of debate. Some have advocated pancreaticoduodenectomy (PD) for all DAs, regardless of location, to ensure wide margin clearance and adequate regional lymphadenectomy.[3–6] In contrast, others have supported the use of segmental resection for tumors of the very proximal or distal duodenum provided margin-negative resection can be achieved.[7–9] Few studies have compared the two surgical approaches directly, but there are those that are limited by their small sample size and single institution design.[5,7,10,11] We sought to investigate the impact of extent of surgery on long-term outcome after resection of DA by utilizing the Surveillance, Epidemiology, and End Results (SEER) database, a large population-based cancer registry.

METHODS

The SEER database was used to identify all patients with adenocarcinoma of the duodenum (topography code C170) diagnosed from 1988–2010. Other periampullary malignancies and those without confirmed histology were specifically excluded. Patients were then divided into two groups based on type of surgery received: simple resection (SR) and radical resection (RR). SR included SEER surgery of primary site codes 30 and 40, which were defined as “simple/partial removal of primary site” and “total surgical removal of primary site.” RR included SEER code

60, which was defined as “partial or total removal of the primary site with a resection in continuity with other organs.” Patients were excluded if they did not undergo surgery, received only local therapies (e.g., fulguration), local excision (e.g., polypectomy or excisional biopsy), debulking, or surgery not otherwise specified or unknown type. We assumed that the RR group was mostly comprised of PD cases, whereas the SR group was mostly comprised of segmental resections of the duodenum.

Descriptive statistics were then calculated for demographics (age, gender, race), clinicopathologic characteristics (tumor grade; TNM stage; American Joint Committee on Cancer [AJCC], 6th edition stage; tumor size; lymph node ratio [LNR]), and treatment (number of LNs examined, radiation). A comparison between the two groups was assessed using χ^2 analysis. Perioperative mortality was defined as death at 1 or 3 months and was compared between groups. At the most recent follow-up, patients were recorded as being alive, dead of disease, or dead of other causes. Cohort and stage-based survival analysis was then performed for both disease-specific survival (DSS) and overall survival (OS) using the Kaplan–Meier method. Statistical significance was assessed using the Mantel-Cox log-rank test. Data were unadjusted for demographic, tumor-related, or treatment variables. Statistics were performed with Graphpad Prism 6.0 (Graphpad Software, Inc., La Jolla, CA, USA).

Univariate and multivariate Cox proportional hazards models were then created to evaluate factors associated with OS. Independent variables included in the univariate model were: age; race; gender; year of diagnosis; histological grade T, N and M stages; AJCC stage; surgery type; tumor size; LNs examined; LNR; and receipt of radiation. The type of surgery and noncollinear variables with $p < 0.2$ on univariate analysis were included in the multivariate model. Missing data were incorporated into the statistical models as separate covariates. Statistics were performed via SPSS, version 20.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

There were 4,037 cases of confirmed DA reported to the SEER database between 1988 and 2010. There were 2,331 cases excluded for undergoing no surgery or an unknown surgery, whereas 81 cases were excluded for undergoing local excision and 14 cases were excluded for debulking. Of the 1,611 patients who met all inclusion criteria, 746 (46.3 %) underwent SR and 865 (53.7 %) underwent RR. Patient characteristics are listed in Table 1. As expected, patients undergoing RR had more poorly differentiated and larger tumors. They were more likely to have advanced N- and T-stage disease and undergo radiation. There were no significant differences in gender or race. We noted a small, clinically insignificant difference in age distribution. Patients undergoing RR had more LNs examined compared to SR (11.0 ± 8.9 vs. 6.8 ± 7.8; $p < 0.0001$) with more positive LNs (2.0 ± 3.1 vs. 1.6 ± 2.7, <0.05). Mean LNR was 0.22 ± 0.3 for SR and 0.19 ± 0.26 for RR ($p = 0.09$). There were no significant differences in 30-day mortality (9.0 vs. 7.9 %; $p = 0.43$) or 90-day mortality (13.0 vs. 12.0 %; $p = 0.54$) for patients undergoing SR versus RR, respectively.

Kaplan–Meier curves were calculated for OS and DSS (Fig. 1). The 5-year DSS rates were 85.0, 60.9, 40.2, and 17.2 %, respectively, for stage I–IV cancers. The 5-year OS rates were 65.9, 50.4, 31.4, and 11.9 %, respectively. There was no significant difference in survival based on surgery type (Fig. 2). Median DSS and OS were 75 and 38 months, respectively, for SR, and 53 and 29 months, respectively for RR. The 5-year DSS and OS rates were 52.8 and 41.3 %, respectively for SR versus 48.8 and 37.6 %, respectively, for RR ($p = 0.31$ for DSS; $p = 0.89$ for OS). When stratified by stage, no significant differences in OS were detected based on extent of the resection (Fig. 3).

On univariate Cox proportional hazards regression analysis, surgery type was not associated with OS (OR 0.98; 95 % CI 0.87–1.11 for RR vs. SR). Increasing age, poor tumor differentiation, increasing tumor stage, nodal stage, AJCC stage, and increasing LNR were all associated with worse OS. Greater number of LNs removed and the receipt of radiation were associated with improved OS, whereas gender, race, and year of diagnosis were not associated with survival (Table 2). After controlling for other factors, type of surgery was not associated with survival (OR 1.11; 95 % CI 0.97–1.27 for RR vs. SR) on multivariate Cox regression analysis (Table 2).

DISCUSSION

Because of its relative rarity, the literature on DA consists primarily of small, retrospective institutional series. This population-based analysis marks one of the largest series of DA and the largest to investigate the impact of extent of resection on outcomes. As expected, patients undergoing RR had tumors of more advanced stage and grade, and a greater number of LNs excised compared to those undergoing SR. However, these differences did not translate into diverse outcomes in either univariate or multivariate analyses. The use of RR (defined as a resection of the primary duodenal tumor en bloc with an adjacent organ) was associated with similar outcomes compared to lesser resections.

TABLE 1 Demographic, clinicopathologic, treatment and follow-up information for patients with primary DA undergoing simple versus radical resection

Characteristics	Total (1,611)	Simple Resection (746)	Radical Resection (865)	p value
Age				0.025
<50	209 (13.0)	90 (12.1)	119 (13.8)	
50–59	286 (17.8)	115 (15.4)	171 (19.8)	
60–69	413 (25.5)	197 (26.4)	216 (25.0)	
70–79	503 (31.2)	233 (31.2)	270 (31.2)	
≥80	200 (12.4)	111 (14.9)	89 (10.3)	
Gender				0.75
Male	745 (46.2)	349 (46.8)	396 (45.8)	
Female	866 (53.8)	397 (53.2)	469 (54.2)	
Race				0.16
White	1,264 (78.5)	585 (78.4)	679 (78.5)	
Black	233 (14.5)	122 (16.4)	111 (12.8)	
Other	114 (7.1)	77 (10.1)	75 (8.7)	
Grade				<0.0001
Well-differentiated	153 (9.5)	89 (12.0)	64 (7.4)	
Moderately-differentiated	816 (50.4)	383 (50.8)	433 (50.1)	
Poorly-differentiated	545 (34.1)	213 (28.9)	332 (38.4)	
Unknown	97 (6.1)	61 (8.3)	36 (4.2)	
Tumor size				<0.0001
<2 cm	154 (9.5)	77 (10.1)	77 (8.9)	
2–4 cm	523 (32.3)	235 (31.5)	288 (33.3)	
>4 cm	690 (42.8)	282 (37.8)	408 (47.2)	
Unknown	246 (15.3)	152 (20.4)	92 (10.6)	
T stage				<0.0001
T1	143 (8.8)	100 (13.2)	43 (5.0)	
T2	152 (9.4)	84 (11.3)	68 (7.9)	
T3	535 (33.2)	308 (41.3)	227 (26.2)	
T4	705 (43.7)	206 (27.6)	499 (57.7)	
Unknown	76 (4.9)	48 (6.4)	28 (3.2)	
N Stage				<0.0001
N0	615 (38.0)	262 (35.1)	353 (40.8)	
N1	488 (30.3)	195 (26.1)	293 (33.9)	
N2	239 (14.8)	81 (10.9)	158 (18.3)	
Unknown	269 (16.7)	208 (27.9)	61 (7.1)	
Stage				<0.0001
I	177 (10.9)	106 (13.9)	71 (8.2)	
II	480 (29.7)	199 (26.7)	281 (32.5)	
III	676 (42.0)	256 (34.3)	420 (48.6)	
IV	116 (7.4)	67 (9.0)	49 (5.7)	
Unknown	162 (10.0)	118 (15.8)	44 (5.1)	
LNs examined				<0.0001
0	237 (14.7)	186 (24.9)	51 (6.0)	
1–6	474 (29.4)	231 (31.0)	243 (28.1)	
7–14	511 (31.7)	191 (25.6)	320 (37.1)	
≥15	316 (19.6)	99 (13.3)	217 (25.2)	
Unknown	73 (4.5)	39 (5.3)	34 (3.9)	
LN ratio				<0.0001
0	615 (38.2)	262 (35.1)	353 (40.8)	

TABLE 1 continued

Characteristics	Total (1,611)	Simple Resection (746)	Radical Resection (865)	p value
<0.2	255 (15.8)	84 (11.3)	171 (19.8)	
0.2–0.4	203 (12.6)	77 (10.3)	126 (14.6)	
>0.4	269 (16.7)	115 (15.4)	154 (17.8)	
Unknown	269 (16.9)	208 (27.9)	61 (7.1)	
Radiation				<0.0001
None	1,335 (82.9)	654 (87.7)	681 (78.7)	
Received	276 (17.1)	92 (12.3)	184 (21.3)	
Perioperative mortality				
30-Day	135 (8.4)	67 (9.0)	68 (7.9)	0.43
90-Day	201 (12.5)	97 (13.0)	104 (12.0)	0.54
Follow-up				
Alive	584 (36.3)	274 (36.7)	310 (35.8)	
Died of disease	693 (43.0)	306 (41.0)	387 (44.7)	
Died of other causes	334 (20.7)	166 (22.3)	168 (19.4)	
Months, mean (range)	41.9 (1–274)	40.1 (0–268)	43.1 (0–274)	

Results are number (%) unless otherwise specified

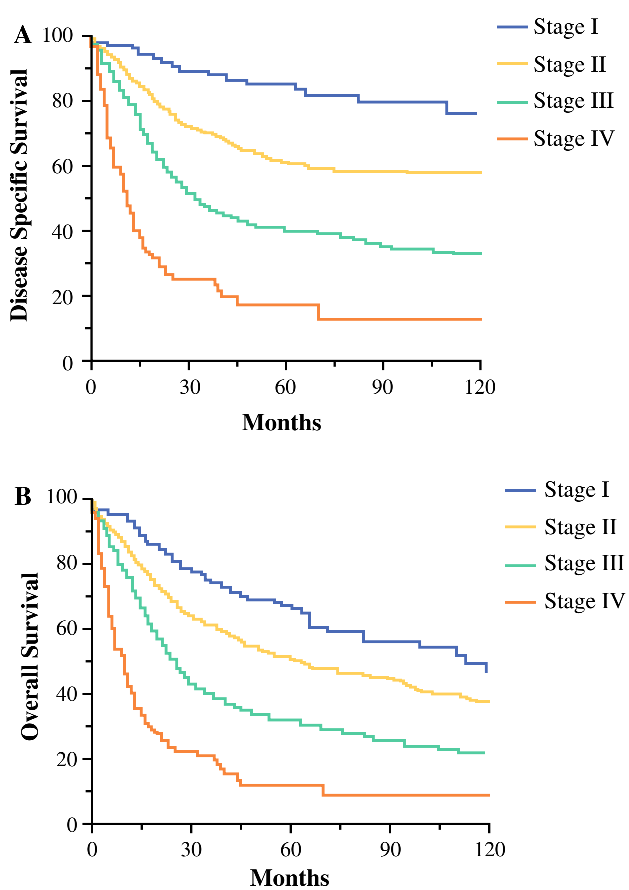

FIG. 1 Stage-based DSS (**a**) and OS (**b**) for patients with DA ($p < 0.0001$ for both)

Investigators have long debated the most oncologically appropriate approach for duodenal cancers. Some have argued that only PD ensures adequate surgical margins and complete regional lymphadenectomy. Most early series reported few long-term survivors of segmental resection for DA.[3,4,12–15] On the basis of these early experiences and theoretical principles, PD was believed to be the preferred approach for resectable DA.[4] Nevertheless, little evidence is available to actually support this notion. Sohn et al.[6] compared 35 patients undergoing PD to 13 patients undergoing pancreas-sparing duodenectomy and found significantly improved long-term survival in the former group (5-year rates, 63 vs. 0 %). However, the segmental resection group in this study had significantly higher rates of positive surgical margins (23 vs. 3 %), therefore, calling the study conclusion into question.[6]

Most other attempts to compare segmental resection with PD have not found one to be superior to the other. Kaklamanos et al.[10] directly compared 26 patients undergoing PD to 11 patients undergoing segmental resection between 1978 and 1998. There was no statistically significant difference in outcomes between the two groups.[10] Lowell et al.[9] reported their experience with segmental resection of five patients with DA of the distal duodenum. Only one patient experienced a postoperative complication and all five patients were alive without evidence of disease at follow-up at 6–87 months.[9] Other authors have reported similar results with SR.[16–19] Bakaeen et al.[11] reviewed their series of 50 patients

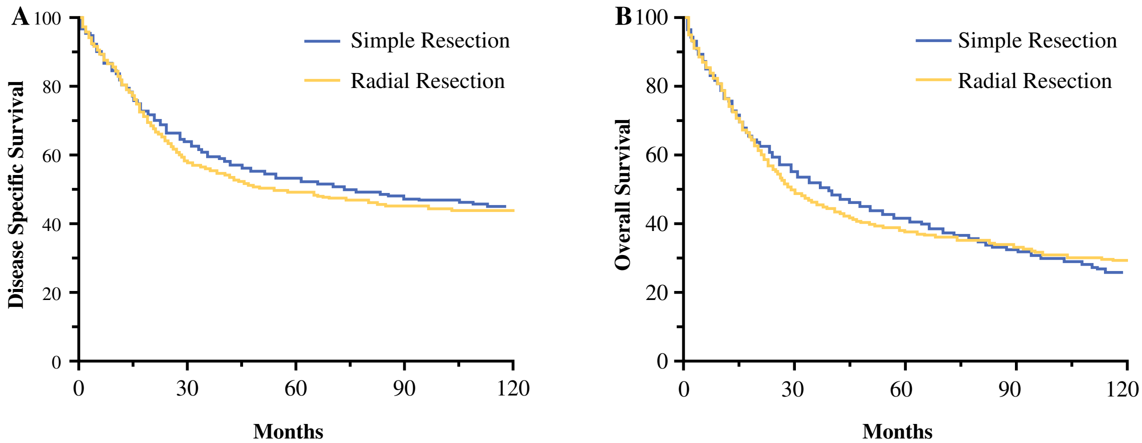

FIG. 2 DSS (**a**) and OS (**b**) for DA based on type of surgery ($p = 0.31$ for DSS and $p = 0.89$ for OS)

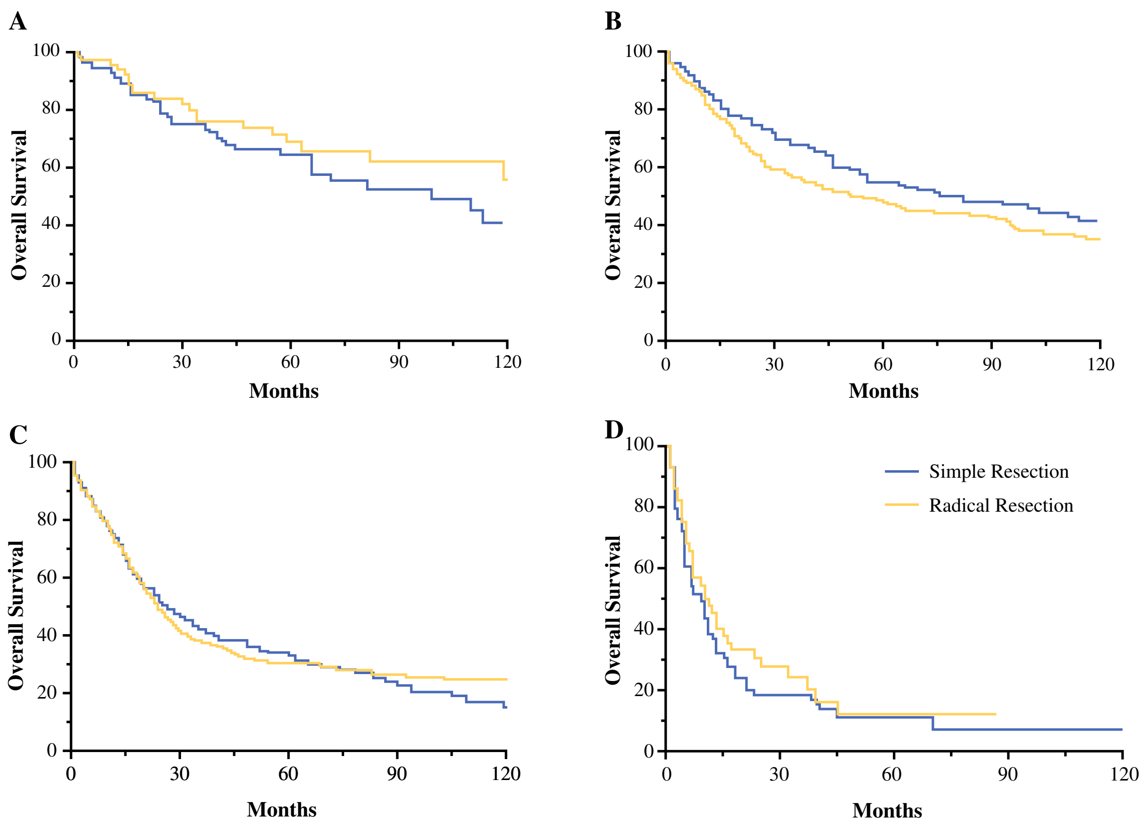

FIG. 3 OS based on type of surgery for stage I (**a**), stage II (**b**), stage III (**c**), and stage IV (**d**) DA ($p = 0.24$ for stage I; $p = 0.1$ for stage II; $p = 0.86$ for stage III; and $p = 0.38$ for stage IV)

undergoing RR compared to 15 patients undergoing limited curative resection and found similar postoperative morbidity, significantly shorter hospital length of stay, and similar OS. Similarly, Tocchi et al.[18] reported their series of 47 patients with DA: 22 underwent palliative bypass, 9 underwent PD, and 16 underwent segmental duodenal resection after intestinal derotation. Patients undergoing segmental resection had shorter length of hospital stay, less postoperative morbidity, and mortality with equivalent long-term outcomes. On the basis of their data, these authors concluded that when negative margins are attainable, segmental resection is the preferred approach. In some cases, PD will remain the preferred operation, regardless of location (e.g., in familial adenomatous polyposis or when negative margins are not possible with a segmental resection).

TABLE 2 Cox proportional hazards regression analysis for OS

Characteristics	Univariate	Multivariate
Age		
<50	–	–
50–59	1.01 (0.79–1.29), 0.72	0.96 (0.75–1.23), 0.75
60–69	1.39 (1.12–1.74), 0.003	1.39 (1.11–1.74), 0.004
70–79	1.89 (1.53–2.34), <0.0001	2.01 (1.62–2.49), <0.0001
≥80	2.32 (1.81–2.97), <0.0001	2.43 (1.89–3.13), <0.0001
Gender		
Male	–	
Female	1.07 (0.94–1.20), 0.31	
Race		
White	–	
Black	0.92 (0.77–1.09), 0.31	
Other	0.92 (0.81–1.05), 0.21	
Year of diagnosis		
1988–1999	–	
2000–2010	0.99 (0.87–1.13), 0.91	
Grade		
Well-differentiated	–	–
Moderately-differentiated	0.97 (0.78–1.21), 0.80	0.93 (0.74–1.16), 0.50
Poorly-differentiated	1.25 (1.0–1.56), 0.053	1.23 (0.97–1.55), 0.09
Unknown	1.04 (0.76–1.43), 0.80	0.85 (0.62–1.18), 0.34
T stage		
T1	–	
T2	1.36 (0.99–1.87), 0.057	
T3	1.37 (1.05–1.79), 0.02	
T4	1.94 (1.50–2.51), <0.0001	
Unknown	4.01 (2.83–5.67), <0.0001	
N stage		
N0	–	
N1	1.61 (1.38–1.88), <0.0001	
N2	2.33 (1.93–2.81), <0.0001	
Unknown	2.13 (1.79–2.54), <0.0001	
Stage		
I	–	–
II	1.36 (1.05–1.76), 0.02	1.59 (1.21–2.08), 0.001
III	2.19 (1.71–2.81), <0.0001	2.61 (2.00–3.39), <0.0001
IV	4.51 (3.26–6.23), <0.0001	5.19 (3.77–7.14), <0.0001
Unknown	2.52 (1.90–3.35), <0.0001	2.08 (1.45–2.98), <0.0001
Surgery		
Simple resection	–	–
Radical Resection	0.98 (0.87–1.11), 0.80	1.11 (0.97–1.27), 0.12
Tumor size		
<2 cm	–	–
2–4 cm	1.39 (1.10–1.75), 0.0061	1.22 (0.96–1.56), 0.10
>4 cm	1.0 (0.80–1.24), 0.99	0.98 (0.77–1.24), 0.84
Unknown	1.59 (1.24–2.05), <0.0001	1.50 (1.16–1.93), 0.002
LNs examined		
0	–	–
1–6	0.74 (0.62–0.88), <0.0001	0.87 (0.65–1.17), 0.35
7–14	0.68 (0.57–0.82), <0.0001	0.74 (0.55–1.0), 0.05

TABLE 2 continued

Characteristics	Univariate	Multivariate
>15	0.57 (0.46–0.70), <0.0001	0.64 (0.46–0.88), 0.007
Unknown	0.76 (0.56–1.03), 0.08	0.85 (0.60–1.21), 0.38
LN ratio		
0	–	
<0.2	1.37 (1.13–1.67), 0.0014	
0.2–0.4	1.76 (1.43–2.18), <0.0001	
>0.4	2.26 (1.88–2.72), <0.0001	
Unknown	2.13 (1.79–2.54), <0.0001	
Radiation		
None	–	–
Received	0.84 (0.72–0.99), 0.04	0.91 (0.77–1.08), 0.29

Results are odds ratio (95 % confidence interval), *p* value

The importance of adequate lymphadenectomy has long been appreciated. Our study found that an increasing number of LNs removed at the time of surgery were associated with improved survival in a step-wise fashion. However, the optimal number of retrieved LNs is not well established. Overman et al.[1] found that increasing lymphadenectomy was associated with improved survival in stage II small bowel adenocarcinoma, however, it did not specifically analyze a threshold of more than seven LNs. Sarela et al.,[20] on the other hand, noted that removal of at least 15 LNs (as is recommended for gastric adenocarcinoma) greatly enhanced the prognostic discriminatory ability of LN status. Although the AJCC guidelines recommend at least six LNs be evaluated for duodenal or small bowel adenocarcinoma, some have questioned whether the minimum number of LNs to be examined should be increased.[21] In our study, RR was associated with a significantly greater number of LNs removed compared to SR, but again this did not equate into long-term survival benefits. One possible explanation may be that the lymphatics of the first or fourth portions of the duodenum may drain into LNs around the pylorus or root of the mesentery, respectively (but not to LNs around the pancreatic head), making PD not to be advantageous for tumors in these locations. Because the SEER database does not contain information on the specific location of the tumor in the duodenum, we were unable to investigate this further.

LN metastasis remains one of the most important prognostic factors for DA.[5,8,10,11,20,22–27] In the largest single institution series of 122 patients who underwent PD for DA, LN involvement was found to be the only significant variable associated with survival on multivariate analysis. The 5-year survival was 68 % for node-negative patients, but only 17 % for those with N2 disease (defined as the presence of four or more positive nodes).[24] Lee et al.[22] calculated a 3-year survival rate of 21 % for patients with nodal disease compared to 87.5 % for node-negative patients. Other studies have found the LNR to be even more predictive of outcomes.[1,24] Similarly, in our study, N stage and LNR were two of the factors most strongly associated with survival.

The role of adjuvant radiation therapy for DA is not well established. In our study, approximately 17 % of patients received radiation therapy, which was more common among those undergoing PD. The use of radiation was associated with improvements in survival on univariate analysis, but this effect disappeared after controlling for other variables. One small study demonstrated an effect of adjuvant chemoradiation on local control compared to historical controls.[28] However, other studies have been unable to reproduce this positive effect of chemoradiation on either local control or OS.[24,29] In the largest single institutional series of resected DA, a similar survival was seen in patients receiving chemoradiation, despite the higher prevalence of nodal disease in this group.[24] Therefore, postoperative radiation may continue to have a role in high-risk patients with positive margins, LN metastases, and locally aggressive tumor biology.

We designed this study to investigate the impact of extent of resection for DA on outcome. Although no differences in survival were seen between SR and RR, we acknowledge several limitations in our analysis. The SEER database does not have specific codes that differentiate between segmental duodenal resection and PD. We inferred that PD cases would be typically coded as RR because the duodenal tumor was resected en bloc with another organ (pancreas) and that segmental resections would be coded as SR. However, as with all registry-based analyses, the accuracy of the aforementioned coding is not perfect. In addition, SEER does not record information on preoperative comorbidities, postoperative complications, adjuvant chemotherapy, and margin status, all of which represent important variables to incorporate in an analysis of this kind. On the other hand, the advantage of the SEER database is that it is a prospectively collected, population-based cancer registry, which captures 26 % of all cancer cases throughout the United States with an impressively maintained follow-up. Its large sample size enables the study of less common diseases. Previous studies on DA have been significantly limited by their small sample size.

In summary, this large population-based study showed that RR (such as in the form of PD) does not appear to confer improved survival compared with simple segmental resection for DA in univariate, multivariate, and stage-by-stage analyses. DA in some situations (such as when the tumor is located in the second portion of the duodenum) requires PD and cannot be technically removed with a lesser resection. In these situations, segmental resection should not be attempted at the expense of proper oncologic surgery. However, our results support the notion that a segmental resection is an appropriate surgical strategy for adenocarcinoma of the duodenum when technically and oncologically feasible and when negative margins can be achieved.

DISCLOSURE None.

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