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The importance of assessing the SMA margin in patients undergoing pancreaticoduodenectomy

Edward Eun Cho, Houssam Osman, Daniel Dietemann, D. Rohan Jeyarajah

ABSTRACT

Aim: The purpose of this study is to examine the true incidence of superior mesenteric artery (SMA) positivity in patients who have superior mesenteric vein (SMV) positivity while undergoing pancreaticoduodenectomy (PD) for pancreatic adenocarcinoma (PDAC). Methods: All patients who underwent PD for PDAC between January 2005 and December 2011 were retrospectively identified from our database. Patients deemed resectable by NCCN guidelines, protocol CT scans, and endoscopic ultrasound were included. The PD specimen was inked using five colors to specifically identify and study the SMV and SMA margins. We also analyzed and compared R1-sub groups (R1A group- SMA and SMV positive; R1B group - SMV positive, SMA negative). Results: 98 patients underwent PD for resectable pancreatic adenocarcinoma. 75 patients (76.5%) were found to have negative surgical margin on final pathology (R0 group) while 23 patients (23.4%) had positive SMV margins (R1 group). In the R1 group, 11 patients (47.8%) were found to have positive SMA margin (R1A group) and 12 patients were SMV positive and SMA negative (R1B group). No statistically significant survival difference was noted between R0 and R1 or between R1-A and R1-B. Conclusion: This study demonstrates that with careful inking of the SMA and SMV margins, there is a high rate of concurrent SMA positivity in those patients that are SMV positive. There was no impact on survival. Accurate margin assessment is critical by careful examination and inking of the SMA and SMV margin.

Keywords: Pancreatic cancer, Pancreaticoduodenectomy, Margin positivity, Superior mesenteric

Edward Eun Cho[1], Houssam Osman[1], Daniel Dietemann[2], D. Rohan Jeyarajah[1,3]

Affiliations: [1]Department of Surgery, Methodist Richardson Medical Center, Dallas, TX, USA; [2]University of North Texas Health Science Center, Fort Worth, TX; [3]Methodist Richardson Cancer Center, 2805 E. President George Busy Hwy, Richardson, TX, USA.

Corresponding Author: D. Rohan Jeyarajah, Methodist Richardson Cancer Center, 2805 E. President George Busy Hwy, Richardson, TX 75082, USA; Email: rohanjeyarajah@gmail.com

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INTRODUCTION

Pancreatic cancer remains a disease with a dismal prognosis. In 2008, there were 37,680 cases diagnosed with 34,290 deaths. With a 5 year survival less than 5%, the onus has been on preoperative and postoperative treatments as an adjunct to surgery to improve survival [1]. Long term survival in pancreatic cancer is determined by many factors including tumor size, lymphovascular invasion, lymph nodes involvement, and margin positivity [2, 3]. While it is a consideration that positive margins may be suggestive of a more biologically

aggressive cancer, recent reports suggest that in the era of multimodality therapy and standardized SMA dissection that an equivalent median survival may be achieved even with positive margin resection [4].

The general descriptors of margin status (R0: no residual tumor, R1: microscopic residual tumor, R2: macroscopic residual tumor) as defined by the American joint Committee on Cancer (AJCC) are broadly used in pathology reports. With careful patient selection, improved imaging, and proper surgical technique, R2 resections are largely avoided. It is rather the R1 resections that frustrate surgical endeavor. As venous resection and reconstruction are introduced to achieve R0 resection in cases of vein involvement, the involvement of superior mesenteric artery margin remains a concern. While the pancreatic and bile duct transection margins can be re-resected if intraoperative frozen section analysis determines that they are positive, the SMA margin cannot be re-excised, as surgeons do not typically resect the SMA when performing PD. There have been several reports that show a high rate of complications in SMA resected PD cases [5].

The aim of this study was to investigate the true success of clearing the SMA margin when the SMV is positive.

MATERIALS AND METHODS

An Institutional Review Board approval was obtained for analysis of a prospectively maintained database of pancreatic cancer patients under care of a single surgical group at the Methodist Health Systems between January 2005 and December 2011. Only patients who were diagnosed with pancreatic head adenocarcinoma and deemed resectable by preoperative imaging were included for analysis. All patients had pancreatic protocol CT scans and preoperative laboratory work including CA 19-9 levels. Endoscopic ultrasound (EUS) was used on selective basis. Borderline resectable disease is defined as tumors that exhibit the following: encasement of a short segment of the hepatic artery, without evidence of tumor extension to the celiac axis, that is amenable to resection and reconstruction; abutment of the SMA involving ≤180° of the circumference of the artery; or short-segment occlusion of the SMV, PV, or SMPV confluence that is amenable to vascular reconstruction because of a normal SMV below and normal PV above the area of tumor involvement. These patients at our institution receive neoadjuvant therapy and were therefore excluded. Resectability was defined by excluding all definitions of borderline resectable pancreatic cancer [6, 7]. The truth is that this definition was somewhat in flux during this study period and therefore there was some heterogeneity in the patient definitions with time. This only allowed patients with a) no extrapancreatic disease, b) no involvement of SMV-Portal vein confluence and c) no evidence of tumor extension to the SMA or celiac axis, as defined by the presence of a tissue plane between the tumor and these structures. Patients who underwent pancreatic resections other than PD (eg, distal pancreatectomy or total pancreatectomy) were also excluded.

Pancreaticoduodenectomy (PD) was performed in fashion previously described by our group. In short we perform a Cattell-Braasch maneuver with early identification of the SMA from its aortic root. Identification of the SMV is through separation of the mesocolon from the head of the pancreas and following the middle colic vessels to the gastro-epiploic trunk. Division of the uncinate process is performed with Harmonic energy shear™ with a posterior SMA first dissection in the majority of cases. The SMA margin is skeletonized to the left of the vessel, but the vessel is not skeletonized for 360°.

Pathology is standardized to a five ink technique with analysis of the margins at the following areas:

1. Pancreas
2. SMV-Portal
3. SMA
4. Bile duct
5. True Retroperitoneal Margin (Figure 1).

Pancreatic and bile duct margins are frozen intra-operatively at the discretion of the surgeon. Postoperative parameters of morbidity included bleeding, intra-abdominal abscess, cardiac events, pulmonary complication and pancreatic leaks as defined by the International Study Group of Pancreatic Surgery (ISGPS) consensus statement were utilized [8]. Morbidity and Mortality were defined within the first 30 days of surgery or the length of hospital stay if exceeding 30 days.

Continuous variables were compared using the unpaired Student's T test or Mann Whitney U test. Categorical variables were compared using either the Pearson Chi-Square or Fisher's exact analysis. Kaplan-Meier curves were used for survival analysis. A p-value of 0.05 was accepted as the level of statistical significance. Statistical analysis was performed on IBM SPSS 20.0 software.

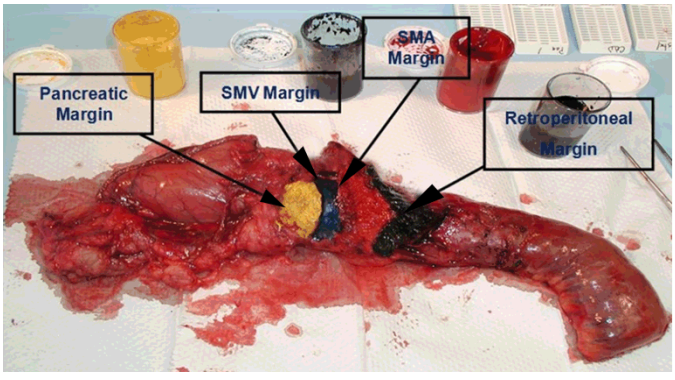

Figure 1: Margin inking for pancreaticoduodenectomy.

RESULTS

Resectable pancreatic cancer with appropriate staging workup was identified in 98 patients. All patients underwent PD. 75 patients were identified who had an R0 resection (R0 group), with 23 patients having an R1 resection with SMV positive margin (R1 group). There was no difference in age, gender, mean comorbid index (modified Charlson-comorbidity parameters) or pathologic stage between these two groups (Table 1). There were no R2 patients. None of the patients had venous or arterial reconstruction. Mean operative time was 3.1 hours (Range 2.2–4.3) for the R1 group which was significantly shorter compared to 3.5 hours (Range 1.4–5.5) for R0 group, p=0.0003. There was no survival difference between the two groups.

Of the 23 patients in R1 group, 11 patients (47.8%) were found to have both SMV and SMA positive margins (R1A group). 12 patients (52.2%) were found to have only SMV positive margin and a SMA negative margin (R1B group). Patient and pathologic characteristic of R1 group are listed in Table 2. All SMA positive patients were SMV positive. When comparing R1A group to R1B, there was no difference in the lymph node positive rate, mean number of lymph nodes examined, mean tumor size, mean operative time, or postoperative morbidity as shown in Table 2.

All patients received comparable regimens of post-operative chemotherapy and radiation (p=0.642). The median survival time for the R0 group was 20.6 months compared to 14 months for the R1 group, p= 0.098 (Figure 2). There was no difference in median survival time between R1A and R1B; 19 months and 10 months respectively, p=0.458 (Figure 3).

DISCUSSION

There has been great debate recently regarding the impact of margin positivity on overall survival and recurrence. It is generally accepted as a fundamental principle of oncologic surgery that a positive surgical margin after resection of a solid tumor is a poor prognostic factor. In this study, 23.4% of patients with pancreatic head adenocarcinoma who were deemed to be resectable on preoperative imaging underwent PD and were found

Table 1: Entire Patient Cohort characteristics

	R0 group SMV Margin Negative (N=75)	R1 group SMV Margin Positive (N=23)	P value
Patient Characteristics			
Male	41 (54.67%)	8 (34.78%)	P=0.095 [NS]
Female	34 (45.33%)	15 (65.22%)	P=0.095 [NS]
Median Age at Surgery (Years)	70 [42–88]	70 [48–84]	P=0.2844 [NS]
Median Charlson Comorbidity Index	6 [3–10]	6 [3–9]	P=0.8047 [NS]
Median ASA Class Index	3 [2–4]	3 [2–4]	P=0.9214 [NS]
Median Length of Hospital Stay (Days)	12 [2–40]	13 [7–24]	P=0.7557 [NS]
Median Body Mass Index (kg/m2)	25.3 [14.3–40.5]	23.4 [17.3–39.2]	P=0.5464 [NS]
Operative Characteristics			
Median Operative Time (hours)	3.45 [1.42–5.49]	3.13 [2.16–4.33]	P=0.0003 [S]
Median Estimated Blood Loss (ml)	400 [100–2500]	350 [200–1500]	P=0.9656 [NS]
Pathologic Characteristics			
T1	2 (2.67%)	0	P=1.000 [NS]
T2	10 (13.33%)	3 (13.04%)	P=1.000 [NS]
T3	62 (82.67%)	19 (82.61%)	P=1.000 [NS]
T4	1 (1.33%)	1 (4.35%)	P=0.416 [NS]
Median Number of Lymph Nodes Examined	18 [2–36]	15 [6–33]	P=0.1352 [NS]
Median Number of Positive Lymph Nodes	2 [0–13]	2 [0–8]	P=0.8124 [NS]
Median Tumor Size (cm)	3 [0.3–5.1]	2.8 [2–6.4]	P=0.6110 [NS]
Post-Operative Morbidity			
Post-Op Morbidity	34 (45.33%)	11 (47.83%)	P =0.834 [NS]
Survival Analysis			
Median Survival Time (days)	618 [95% CI = 418; 834]	421 [95% CI = 306; 606]	0.0989 [NS]

Table 2: R1 Group (SMV Margin Positive) characteristics

	R1-A (SMV Positive & SMA Positive) N=11	R1-B (SMV Positive & SMA Negative) N=12	P value
Patient Characteristics			
Male	6 (54.55%)	2 (16.67%)	P=0.089 [NS]
Female	5 (45.45%)	10 (83.33%)	P=0.089 [NS]
Age at Surgery (Years)	64 [55-80]	73 [48–84]	P=0.6482[NS]
Median Charlson Comorbidity Index	6 [4–8]	6.5 [3–9]	P=0.6949 [NS]
Median ASA Class	3 [3–4]	3 [2–4]	P=0.0446 [S]
Median Length of Stay (days)	14 [8–24]	11 [7–23]	P=0.1066 [NS]
Median Body Mass Index	24.9 [19.7–39.2]	22.4 [17.3–36.7]	P=0.2184 [NS]
Operative Characteristics			
Median Operative Time (hours)	3.23[2.16–4.05]	3.04 [2.2–4.33]	P=0.8546 [NS]
Median Estimated Blood Loss (ml)	550 [200–800]	300 [200–1500]	P=0.0805 [NS]
Pathologic Stage			
Pathologic T1	0	0	
Pathologic T2	1 (9/09%)	2 (16.67%)	P=1.000 [NS]
Pathologic T3	9 (81.82%)	10 (83.33%)	P=1.000 [NS]
Pathologic T4	1 (9.09%)	0	P=0.478 [NS]
Median Number of Lymph Nodes Examined	16 [6–24]	13.5 [7–33]	P=0.6639 [NS]
Median Number of Positive Lymph Nodes	2 [0–5]	2.5 [0–8]	P=0.5348[NS]
Median Tumor Size (cm)	2.8 [2.2–4]	2.9 [2–6.4]	P=0.7796 [NS]
Positive Pancreatic Duct Margin	3 (27.7%)	3 (25%)	P=1.000 [NS]
Positive Bile Duct margin	0	1 (8.33%)	P=1.000 [NS]
Post-Operative Morbidity			
Pancreatic Leak	1 (9.09%)	0	P=0.478 [NS]
Post-Op Morbidity	6 (54.55%)	5 (41.67%)	P =0.684 [NS]
Survival Analysis			
Median Survival Time (days)	583 [95% CI = 306; 648]	313	0.4583 [NS]

to have SMV positive margin on final pathology. 47.8% of these patients were found to have positive margin at the SMA as well. There was no statistically significant survival difference between negative margin (R0) and microscopically positive margin (R1) patients.

Although multiple studies have shown that R0 resection is associated with a significantly longer median overall survival than R1/R2 resection [9–11], this has recently been cast into doubt by Raut et al. In their analysis of 360 patients with a median follow up of 51.9 months, after stratifying their patient group by R0 (60 patients) versus R1 (300 patients) resection, the study showed that median survival was 27.8 months for the R0 group versus 21.5 months in the R1 group (p=0.026), which was significant on univariate analysis but lost significance on multivariate analysis. The study concluded that there was no significant difference in patient survival or recurrence based on resection margin [4]. Their group of patients, however, included borderline resectable disease patients and both the R0 and R1 groups were heavily pretreated with preoperative regimens (71.9% versus 65%, p=0.28) with a large percentage needing vascular resection (33% versus 50% p=0.01).

When microscopic disease is noted at the pancreatic duct or common bile duct margin, surgical resection can be further extended to obtain a negative margin. For example, the presence of SMV positive margin can be cleared with vein resection and reconstruction. Previous reports documented the safety of vascular reconstruction but a recent retrospective cohort analysis of more than 3000 patients by Castleberry et al documented a significant increase in risk-adjusted 30-day postoperative mortality in the vascular resection group (5.7%) when compared to standard PD (2.9%). In the same study, the vascular resection group was found to have significantly increased overall morbidity (39.9%) when compared to

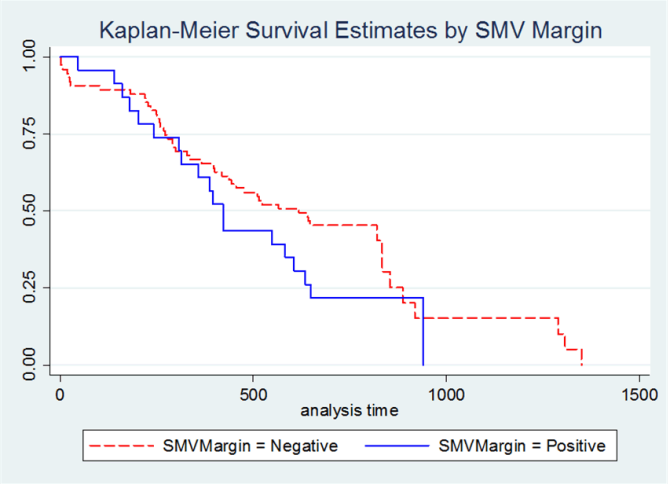

Figure 2: Kaplan-Meier Survival Estimate R0 vs. R1 survival curve.

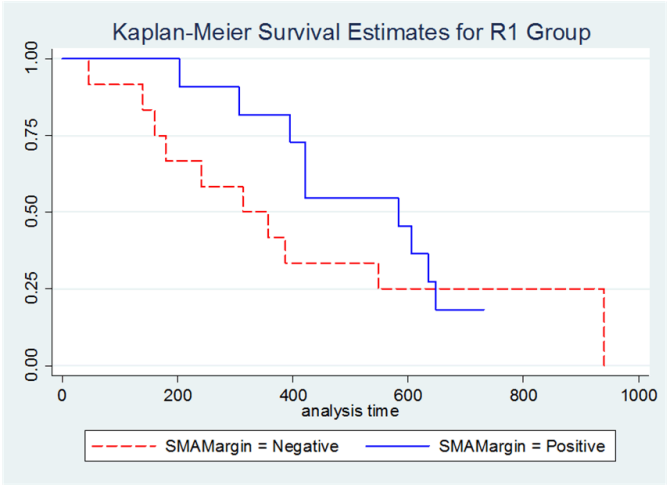

Figure 3: Kaplan-Meier Survival Estimate R1-A vs. R1-B survival curve.

standard PD group (33.3%) [12]. The added morbidity of vein resection combined with the presence of positive SMA margin in almost half the patients with SMV margin positivity and the comparable survival between R0 and R1 resections demonstrated in this study and other previous studies creates the argument against potential benefit of vein resection during PD. It is not the authors' preference to be aggressive with vein resection and so there is no data on those patients that could have undergone SMV resection. This data should hopefully provide a pause in those that routinely perform vein resections in the setting of this high rate of unrecognized SMA positivity.

The SMA first approach is gaining popularity with small retrospective studies showing its safety and efficacy in dealing with certain bulky pancreatic head tumors [13]. The authors' surgical technique during PD is to clear the mesopancreas at the SMA, essentially cleaning the tissue while the specimen is being resected. However, even with pristine surgical technique, our study points out that even when a complete SMA dissection is performed, with no palpable or visible evidence of tumor intraoperatively, a microscopically positive margin of resection may occur due to the infiltrative nature of pancreatic adenocarcinoma.

As the ESPAC 1 and RTOG9704 trials showed, R1 margins of 19–40% are well within the norm of the literature in non-preoperatively treated PD [11, 14]. Verbeke et al described a positive margin rate of 80% in a historical matched comparison [9]. This astonishing margin positivity was further validated by using the standardized Leeds pathology protocol (LEEPP) on a larger, prospective cohort. In a series of 83 patients, the R1 rate for pancreatic cancer was 83%, with margin positivity correlating with decreased survival (p=0.006) [15]. This is further augmented by the fact that a meaningful R0 resection may require clearance of at least 1 mm, which would further increase the rate of R1 resection in past published series if the specimens were examined again [16].

It is difficult to predict whether the patient without gross involvement of the vasculature on preoperative imaging will go on to have an R1 resection. In this study, the shorter operative time in the R1 group reflects that these patients did not have evidence of gross vascular involvement on preoperative workup which usually increases the duration of PD. This leads to the question of whether patients who present with resectable pancreatic head cancer should undergo resection first, accepting the higher rate of R1 resection described in this study or if all patients, even with resectable disease, should undergo neoadjuvant treatment to hopefully shrink the tumor and increase the chances of margin negativity on resection. The upside to this method would be shrinkage of the tumor in question if patient responds to therapy and a higher likelihood of R0 resection at the time of surgery. The limitation is that we may lose the window for resection for a resectable patient by delaying surgery.

Despite minimally invasive options, open Whipple still is the gold standard for surgical treatment of pancreatic head cancer. And these minimally invasive procedures depend on the outcome analysis from our open procedures as a standard for comparison so that we can equal or better the results. Our open Whipple data shows an alarmingly high margin positivity rate and it also shows a concurrent high SMA margin positivity rate in those with positive SMV margins. From our literature search, this has never been reported before. If the margin status is this high in open procedures, how high is it in a minimally invasive procedure?

We are currently looking through our data set with robotic Whipples to answer this question.

Overall, the authors present data to support a high and unrecognized risk of SMA positivity in patients undergoing PD for PDAC when the SMV margin is positive. We would support a more aggressive inking and sampling technique in all specimens examined in patients undergoing PD. We would also advocate for

an adoption of a standardized protocol such as LEEPP across all centers for uniform pathological examination of the surgical specimen. Accurate reporting of margin status is critical to understanding the impact of surgery in patients with pancreatic head cancer.

CONCLUSION

We also hope that this and other data regarding margin status after open PD would be a valuable point of reference in future studies looking at margin status after minimally invasive PD resections or after neoadjuvant treatment is valuable as a point of reference and comparison to future data regarding margin positivity after minimally invasive PD resections.

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Author Contributions

Edward Eun Cho – Substantial contributions to conception and design, Analysis and interpretation of data, Drafting of the article, Final approval of the version to be published

Houssam Osman – Substantial contributions to conception and design, Analysis and interpretation of data, Final approval of the version to be published

Daniel Dietemann – Substantial contributions to conception and design, Analysis and interpretation of data

D. Rohan Jeyarajah – Substantial contributions to conception and design, Analysis and interpretation of data, Drafting of the article, Final approval of the version to be published

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this case report.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.