How Are Pancreas Cancer Surgery Outcomes Affected by Tumor Board Decisions?

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Abstract

Background

Tumor board review of complex patients is an important factor for quality and safety. In this study, we compare the surgical outcomes of patients presented at two gastrointestinal cancer-specific tumor boards within a large healthcare system. Site A represents an academic-type tumor board with a focus on neoadjuvant therapy, whereas Site B represents a community-type tumor board with a primary surgical approach.

Methods

From 2015 through 2020, tumor board patients in Site A (27 patients) and Site B (31 patients) who underwent curative surgical resection were retrospectively compared. Pre-operative variables and pathologic outcomes were reviewed. Additionally, as a surrogate marker of multi-disciplinary care and discussion, the evaluation of a patient by an oncologist before surgery was recorded.

Results:

The use of neoadjuvant therapy was higher at Site A than Site B (52% vs. 10%). Site A had a lower perineural invasion (59% vs. 84%, $p=0.048$), and greater treatment effect identified through surgical pathology ($p<0.009$), accounted for by the greater use of neoadjuvant therapy. Additionally, patients at Site A had a lower percentage of close or positive margins (25.9% vs. 38.7%, $p=0.30$) though both not statistically significant. More patients died within 30 days of surgery at Site B (12.9% vs 3.7% patient, $p=0.35$), though not statistically significant. Site A patients were more likely to be seen by at least one oncologist (medical or radiation) after the tumor board, but before surgery, than at Site B (67% vs 42%).

Conclusion:

These findings suggest that a multi-disciplinary, neoadjuvant therapy approach within a tumor board results in better surgical outcomes. With the implementation of the RO-APM and value-based care, data such as these will need to be applied across large healthcare systems to optimize tumor boards, especially in the community setting.

Introduction

Modern cancer care is complex and involves many healthcare professionals. Multidisciplinary care is an integrated team approach involving specialists to develop an individualized plan for each patient.[1] This approach to cancer treatment is recommended in guidelines from various healthcare organizations, such as the National Comprehensive Cancer Network (NCCN).[2,3] One of the most important aspects of this method is the use of multidisciplinary tumor boards (MDTBs).[4,5]

During MDTBs, complex cancer cases are discussed by numerous healthcare professionals, including medical oncologists, radiation oncologists, surgical oncologists, radiologists, and pathologists, among others. Through collaboration and discussion, healthcare professionals use MDTBs to optimize outcomes for their patients. In these meetings, all participants review the diagnostic work-up and discuss potential treatment options, contributing their specific expertise.[1,4,5] MDTBs have been used frequently for complex gastrointestinal cancers, such as pancreatic adenocarcinomas. Pancreatic adenocarcinomas are among the most aggressive cancers, as the fourth leading cause of cancer death with a five-year survival rate of 9%.[3] Depending on their stage and resectability, different treatment options may be used, such as surgical resection, radiation therapy, and chemotherapy.[2,3,6]

In this study, the target patient population included patients with pancreatic adenocarcinomas who were seen at two gastrointestinal cancer MDTBs within the same large

healthcare system. One of these sites, Site A, represents an academic-type tumor board with a focus on neoadjuvant therapy. The other site, Site B, represents a community-type tumor board with a primary surgical approach. The primary focus of this study was to determine if oncologic outcomes were driven by the tumor board approach. Differences in outcomes based on neoadjuvant versus upfront surgery approaches may lead to policy changes within this hospital system to improve patient care.

Methods

This is a retrospective IRB-approved study of pancreatic adenocarcinoma patients evaluated at a MDTB at either Site A or Site B between 2015 and 2020. All of the patients included in this study underwent a pancreaticoduodenectomy, also known as a Whipple procedure, after being seen at their respective MDTB. Demographic information, tumor location and staging, tumor board results, neoadjuvant therapies, and surgical outcomes were collected for each patient. Regarding surgical outcomes, both clinical and pathologic outcomes were documented. Clinical outcomes that were collected included progression-free survival, overall survival, and 30-day mortality. Surgical pathology results that were collected included margin positivity, grade, TMN staging, number of lymph nodes that were removed, number of positive nodes, perineural invasion, lymphovascular space invasion, and treatment effect (determined by the pathologist while examining the surgical biopsy). Additionally, as a surrogate marker of multi-disciplinary care and discussion, the evaluation of a patient by an oncologist (medical and/or radiation) before surgery was recorded.

Statistical Analysis

Wilcoxon Rank sum was used to compare continuous variables and Chi-squared/Fisher's Exact was used to compare categorical variables. A p-value equal to or less than 0.05 was considered statistically significant.

Results

A total of 58 patients were included, with 27 patients at Site A and 31 patients at Site B. The average age of patients at Site A and Site B was 67.6 at both sites (Figure 1). Of the 27 patients seen at Site A, 13 patients had no treatment before surgery and 14 patients had some form of neoadjuvant therapy before surgery. Of the 31 patients seen at Site B, 28 had no treatment before surgery and 3 patients had neoadjuvant therapy. At Site A, 74.0% of patients were male and at Site B, 45% of patients were male.

Notably, at Site A, 51.9% of patients had neoadjuvant therapy while at Site B, 9.7% of patients had neoadjuvant therapy. Patients at Site A also were more likely to have seen an oncologist (medical or radiation) before surgery (66.7%), compared to Site B (41.9%). Site B had more patients with a higher tumor stage (38.7% at stage III) compared to Site A (7.1% at stage III). Postoperatively, patients at Site A had a lower rate of perineural invasion (59.3%) compared to Site B (83.9%) (p=0.036) (Figure 2). The treatment effect was more apparent in the surgical pathology report in patients from Site A (33.3%) compared to Site B (6.45%) (p=0.009). The 30-day mortality at Site A was 3.7% vs. 12.9% at Site B (p=0.36), though not statistically significant.

The two different sites were also analyzed together to compare the impact of neoadjuvant therapy to no prior therapy within the same hospital system. In Site A and B combined, patients that underwent neoadjuvant therapy had a lower rate of margin positivity (11.8%) compared to patients that did not undergo neoadjuvant therapy (41.5%) (p=0.03) (Figure 3). A similar trend

was seen concerning lymphovascular invasion. In all patients at both sites, patients who underwent neoadjuvant therapy had a lower incidence of lymphovascular invasion (5.9%) compared to those who did not undergo therapy (48.8%) (p=0.002).

Since the mean follow up period was nearly twice as long for Site A than Site B, a Kaplan-Meier Curve was produced, comparing overall survival between the two sites and also comparing overall survival for all patients who received neoadjuvant therapy compared to those who did not (Figure 4).

Discussion

In this cohort of 58 patients between two different sites, the contrasting approaches in these separate tumor boards resulted in different treatments and outcomes. Site A, representing an academic-type tumor board with a focus on neoadjuvant therapy, patients received neoadjuvant therapy 51.9% of the time. Site B, representing a community type tumor board with a primary surgical approach, had patients receiving neoadjuvant therapy 9.7% of the time. This resulted in different pathologic outcomes, such as differences in perineural invasion and presence of treatment effect at the time of surgery.

Previous studies have focused on the variability seen in different tumor boards. In 2013, Kirkegard et al. looked at 19 patients with pancreatic cancer who were each discussed at seven separate MDTBs.[7] There was a significant level of variability in how the different MDTBs viewed resectability. Seven of the patients were deemed to be resectable by one MDTB but unresectable by another. Additionally, in only nine of the 19 patients, the MDTBs all agreed on either a curative or palliative approach to care. One of the points of the discussion noted in this study was that there may be differences in each tumor board with respect to tradition and expertise.[7] This could cause certain tumor boards to be less likely to recommend surgery in

patients with borderline resectable tumors. This theory presented by Kirkegard et al. demonstrates the phenomenon seen in the current study, where Site A and Site B had historically different approaches to pancreatic cancer care.

The positive impact of neoadjuvant therapy on pancreatic cancers has been studied and documented. Nanda et al. followed 29 patients with locally advanced pancreatic cancers that were treated using a modified FOLFIRINOX chemotherapy followed by radiation with concurrent gemcitabine or capecitabine.[6] Roughly half of these patients were unresectable at presentation and were followed up for a median of 15.2 months. After neoadjuvant therapy, 41% of patients were able to undergo surgical resection and of those who underwent resection, 83% had an R0 resection.[6] McClaine et al. found similar results in 26 patients with borderline resectable pancreatic cancer that underwent neoadjuvant therapy.[8] Of those who underwent neoadjuvant therapy and surgical resection, 67% had margin-negative surgical resection and the median survival length was 23.3 months.[8] McClaine et al. found that, in this cohort, patients with borderline resectable pancreatic cancer that were treated with neoadjuvant therapy had similar margin-positivity rates and survival times to those with initially resectable disease. Findings like these are encouraging with regards to the approach of treating borderline resectable cancers with neoadjuvant therapy first, rather than surgery without any prior treatment.

The differences in treatment approaches between Site A and Site B did result in notable outcomes seen in surgical pathology. Site A, which favored neoadjuvant treatment, had a majority of patients receive treatment before surgery and had a higher percentage of patients see a medical or radiation oncologist before surgery. Patients from Site A, in turn, had a lower rate of perineural invasion compared to patients from Site B. Perineural invasion has been regarded as one of the more important prognostic factors in pancreatic cancer, as it increases as the tumor

becomes progressively more undifferentiated.[9] Moreover, perineural invasion has also been associated with increased pain generation in pancreatic cancer.[10]

The higher rate of treatment effect seen in surgical pathology from Site A can be attributed to the use of neoadjuvant therapy. While this may be expected given the tendency at Site A to opt for neoadjuvant therapy, it does indicate that this decision does have a successful treatment effect on the tumor. Through this effect, neoadjuvant therapy can cause a tumor to regress from a borderline resectability classification to one that is resectable. While not statistically significant, there were four patients at Site B who died within 30 days of surgery compared to one patient at Site A. The sample size of this study limited the ability to further assess this but future studies with a larger cohort could examine this in more depth.

These findings do suggest that a multidisciplinary tumor board with a neoadjuvant approach results in better patient outcomes. Specifically, within this hospital system, the results taken from Site A, an academic-type tumor board, can be used to drive a potential policy change throughout the entire hospital system. To support this, when Site A and B were examined together, all patients who underwent neoadjuvant therapy had a much lower incidence of positive surgical margins compared to those who did not undergo neoadjuvant therapy. This was also seen in lymphovascular invasion, which is another useful prognostic tool in cancer management. These findings suggest that, in the larger context of the hospital system, applying an approach favoring neoadjuvant therapy could result in greater patient outcomes.

This study was limited by the small sample size. Both Site A and Site B had small, yet comparable, sample sizes, which made it difficult to obtain a complete analysis of all the variables assessed. This study was also retrospective in nature, which limited certain areas of data collection and prevented any type of control during the study.

With the implementation of the RO-APM and value-based care, data such as these will need to be applied across large healthcare systems to optimize tumor boards, especially in the community setting. These findings suggest that a multi-disciplinary, neoadjuvant therapy approach within a tumor board results in improved surgical outcomes. While the limitations of a small, retrospective dataset are acknowledged, these data support optimizing tumor board structures, especially in the community setting. With the implementation of the RO-APM and value-based care, data such as these will be vital for the management of large healthcare systems.

1. El Saghir NS, Keating NL, Carlson RW, Khoury KE, Fallowfield L. Tumor Boards: Optimizing the Structure and Improving Efficiency of Multidisciplinary Management of Patients with Cancer Worldwide. *American Society of Clinical Oncology Educational Book*. 2014;(34):e461-e466. doi:10.14694/EdBook_AM.2014.34.e461

2. Brauer DG, Strand MS, Sanford DE, et al. Utility of a Multidisciplinary Tumor Board in the Management of Pancreatic and Upper Gastrointestinal Diseases: an Observational Study. *HPB (Oxford)*. 2017;19(2):133-139. doi:10.1016/j.hpb.2016.11.002

3. Kumar R, Herman J, Wolfgang C, Zheng L. Multidisciplinary Management of Pancreatic Cancer. *Surgical Oncology Clinics of North America*. 2013;22(2):265-287.

4. AlFarhan HA, Algwaiz GF, Alzahrani HA, et al. Impact of GI Tumor Board on Patient Management and Adherence to Guidelines. *J Glob Oncol*. 2018;4. doi:10.1200/JGO.17.00164

5. Specchia ML, Frisicale EM, Carini E, et al. The impact of tumor board on cancer care: evidence from an umbrella review. *BMC Health Serv Res*. 2020;20. doi:10.1186/s12913-020-4930-3

6. Nanda RH, El-Rayes B, Maithel SK, Landry J. Neoadjuvant modified FOLFIRINOX and chemoradiation therapy for locally advanced pancreatic cancer improves resectability. *Journal of Surgical Oncology*. 2015;111(8):1028-1034. doi:10.1002/jso.23921

7. Kirkegård J, Aahlin EK, Al-Saiddi M, et al. Multicentre study of multidisciplinary team assessment of pancreatic cancer resectability and treatment allocation. *Br J Surg*. 2019;106(6):756-764. doi:10.1002/bjs.11093

8. McClaine RJ, Lowy AM, Sussman JJ, Schmulewitz N, Grisell DL, Ahmad SA. Neoadjuvant therapy may lead to successful surgical resection and improved survival in patients with borderline resectable pancreatic cancer. *HPB*. 2010;12(1):73-79. doi:10.1111/j.1477-2574.2009.00136.x

9. Liu H, Ma Q, Xu Q, et al. Therapeutic Potential of Perineural Invasion, Hypoxia and Desmoplasia in Pancreatic Cancer. *Curr Pharm Des*. 2012;18(17):2395-2403.

10. Bapat AA, Hostetter G, Von Hoff DD, Han H. Perineural invasion and associated pain in pancreatic cancer. *Nature Reviews Cancer*. 2011;11(10):695-707. doi:10.1038/nrc3131

	Site A		Site B		
Variables	No treatment prior to surgery (n=13)	Treatment prior to surgery (n=14)	No treatment prior to surgery (n=28)	Treatment prior to surgery (n=3)	p-value

Age, years (median, IQR)	69 (59, 76)	70.5 (65, 75)	68 (64.5, 71)	69 (54, 71)	0.79
Gender (male, %)	9 (69.2)	11 (78.6)	12 (42.9) d	2 (66.7)	0.12
Site of Organ (n, %)					0.62
Head	10 (76.9)	11 (78.6)	21 (75.0)	3 (100.0)	
Body	2 (15.4)	0 (0.0)	5 (17.9)		
Tail	0 (0.0)	2 (14.3)	1 (3.57)		
Neck	1 (7.69)	1 (7.14)	1 (3.57)		
Resectability (n, %)					0.001
Resectable	11 (84.6)	5 (35.7) a	23 (82.1) d		
Borderline resectable	1 (7.69)	8 (57.1)	3 (10.7)	3 (100.0) c, f	
Unresectable/metastatic	1 (7.69)	1 (7.14)	2 (7.14)		
Stage (n, %)					0.076
I	3 (23.1)	2 (14.3)	5 (17.9) b		
II	10 (76.9)	8 (57.1)	12 (42.9)	2 (66.7)	
III	0 (0.0)	2 (14.3)	11 (39.3)	1 (33.3)	
Iv	0 (0.0)	2 (14.3)	0 (0.0)		
Work-Up (n, %)					0.60
CT	5 (38.5)	3 (21.4)	12 (42.9)	1 (33.3)	
CT + CA-19	8 (61.5)	11 (78.6)	16 (57.1)	2 (66.7)	
Seen Rad/Onc DR prior to Surgery (yes, %)	4 (30.8)	14 (100.0) a	10 (35.7) d	3 (100.0)	<0.0001

Figure 1. Patient demographics for Site A and Site B. Kruskal-Wallis Test to compare continuous variables. Chi-squared Fisher's Exact to compare categorical variables.

[a] Statistically significant pairwise comparison between group 1 vs 2 without Bonferroni Correction (p<0.05)
[b] Statistically significant pairwise comparison between group 1 vs 3 without Bonferroni Correction (p<0.05)
[c] Statistically significant pairwise comparison between group 1 vs 4 without Bonferroni Correction (p<0.05)
[d] Statistically significant pairwise comparison between group 2 vs 3 without Bonferroni Correction (p<0.05)
[e] Statistically significant pairwise comparison between group 2 vs 4 without Bonferroni Correction (p<0.05)
[f] Statistically significant pairwise comparison between group 3 vs 4 without Bonferroni Correction (p<0.05)

Variables	Site A N=27	Site B N=31	p-value
Follow Up Period (mean, SD)	22.4 (14.6)	13.7 (9.6)	0.009
Margins (Positive, %)	7 (25.9)	12 (38.7)	0.30
30-Day Mortality (yes, %)	1 (3.70)	4 (12.9)	0.36
Disease Progressed (yes, %)	14 (51.9)	16 (51.6)	1.0
Grade (n, %)			0.14
0	2 (7.41)	0 (0.0)	
1	3 (11.1)	6 (19.4)	
2	10 (37.0)	17 (54.8)	
3	12 (44.4)	8 (25.8)	
T stage (n, %)			0.007
0	2 (7.41)	0 (0.0)	
1	4 (14.8)	3 (9.68)	
1b	0 (0.0)	2 (6.45)	
2	7 (25.9)	19 (61.3)	
3	14 (51.9)	6 (19.4)	
4	0 (0.0)	1 (3.23)	
N stage (n, %)			0.28
0	12 (44.4)	9 (29.0)	
≥1	15 (55.6)	22 (70.9)	
Perineural Invasion (present, %)	16 (59.3)	26 (83.9)	0.045
Lymphovascular Invasion (present, %)	8 (29.6)	13 (41.9)	0.42
Treatment (n, %)			
Absent/Not identified	5 (18.5)	1 (3.23)	0.18
No Known Pre-Surgical therapy	0 (0.0)	28 (90.3)	<0.0001
No prior treatment	13 (48.2)	0 (0.0)	<0.0001
Present	9 (33.3)	2 (6.45)	0.009
Hospital Length of Stay, days (median, IQR)	10 (7, 14)	9 (6, 13)	0.25
Number of Nodes Removed (median, IQR)	18 (12, 24)	18 (15, 27)	0.22
Number of Positive Nodes (median, IQR)	1 (0, 4)	2 (0, 6)	0.29

Figure 2. Post-operative pathology results for Site A and Site B. Wilcoxon Rank Sum to compare continuous variables. Chi-squared Fisher's Exact to compare categorical variables. Treatment effect was determined by the pathologist while analyzing the surgical biopsy. Absent/not identified were patients who had neoadjuvant therapy but no treatment effect was seen. Present treatment effect indicated that neoadjuvant therapy had a positive effect on the tumor cells.

Variables	Overall N=58	No treatment prior to surgery (n=41)	Treatment prior to surgery (n=17)	p-value
Margins (Positive, %)	19 (32.8)	17 (41.5)	2 (11.8)	0.034
30-Day Mortality (yes, %)	5 (8.62)	5 (12.2)	0 (0.0)	0.31
Disease Progressed (yes, %)	30 (51.7)	23 (56.1)	7 (41.2)	0.39
Grade (n, %)				0.17
0	2 (3.45)	6 (14.6)	2 (11.8)	
1	9 (15.5)	19 (46.3)	3 (17.7)	
2	27 (46.6)	16 (39.0)	8 (47.1)	
3	20 (34.5)	0 (0.0)	4 (23.5)	
T stage (n, %)				0.066
0	2 (3.45)	0 (0.0)	2 (11.8)	
1	7 (12.1)	3 (7.32)	4 (23.5)	
1b	2 (3.45)	1 (2.44)	1 (5.88)	
2	26 (44.8)	20 (48.8)	6 (35.3)	
3	20 (34.5)	16 (39.0)	4 (23.5)	
4	1 (1.72)	1 (2.44)	0 (0.0)	
N stage (n, %)				0.13
0	21 (36.2)	12 (29.3)	9 (52.9)	
≥1	37 (63.8)	29 (70.7)	8 (47.1)	
Perineural Invasion (present, %)	42 (72.4)	32 (78.1)	10 (58.8)	0.20
Lymphovascular Space Invasion (present, %)	21 (36.2)	20 (48.8)	1 (5.88)	0.002
Treatment (n, %)				
Absent/Not identified	6 (10.3)	0 (0.0)	6 (35.3)	0.001
No Known Pre-Surgical therapy	28 (48.3)	28 (68.3)	0 (0.0)	<0.0001
No prior treatment	13 (22.4)	13 (31.7)	0 (0.0)	0.006
Present	11 (18.9)	0 (0.0)	11 (64.7)	<0.0001
Hospital Length of Stay, days (median, IQR)	9 (7, 14)	9.4 (7, 14)	7 (7, 11)	0.58
Number of Nodes Removed (median, IQR)	18 (13, 24)	18 (14, 25)	17 (12, 21)	0.22
Number of Positive Nodes (median, IQR)	1.5 (0, 4)	2 (0, 4)	0 (0, 3)	0.12

Figure 3. Post-operative outcomes for patients who had neoadjuvant therapy compared to patients who did not have neoadjuvant therapy, Sites A and B combined. Wilcoxon Rank Sum to compare continuous variables. Chi-squared Fisher's Exact to compare categorical variables. Treatment effect was determined by the pathologist while analyzing the surgical biopsy. Absent/not identified were patients who had neoadjuvant therapy but no treatment effect was seen. Present treatment effect indicated that neoadjuvant therapy had a positive effect on the tumor cells.

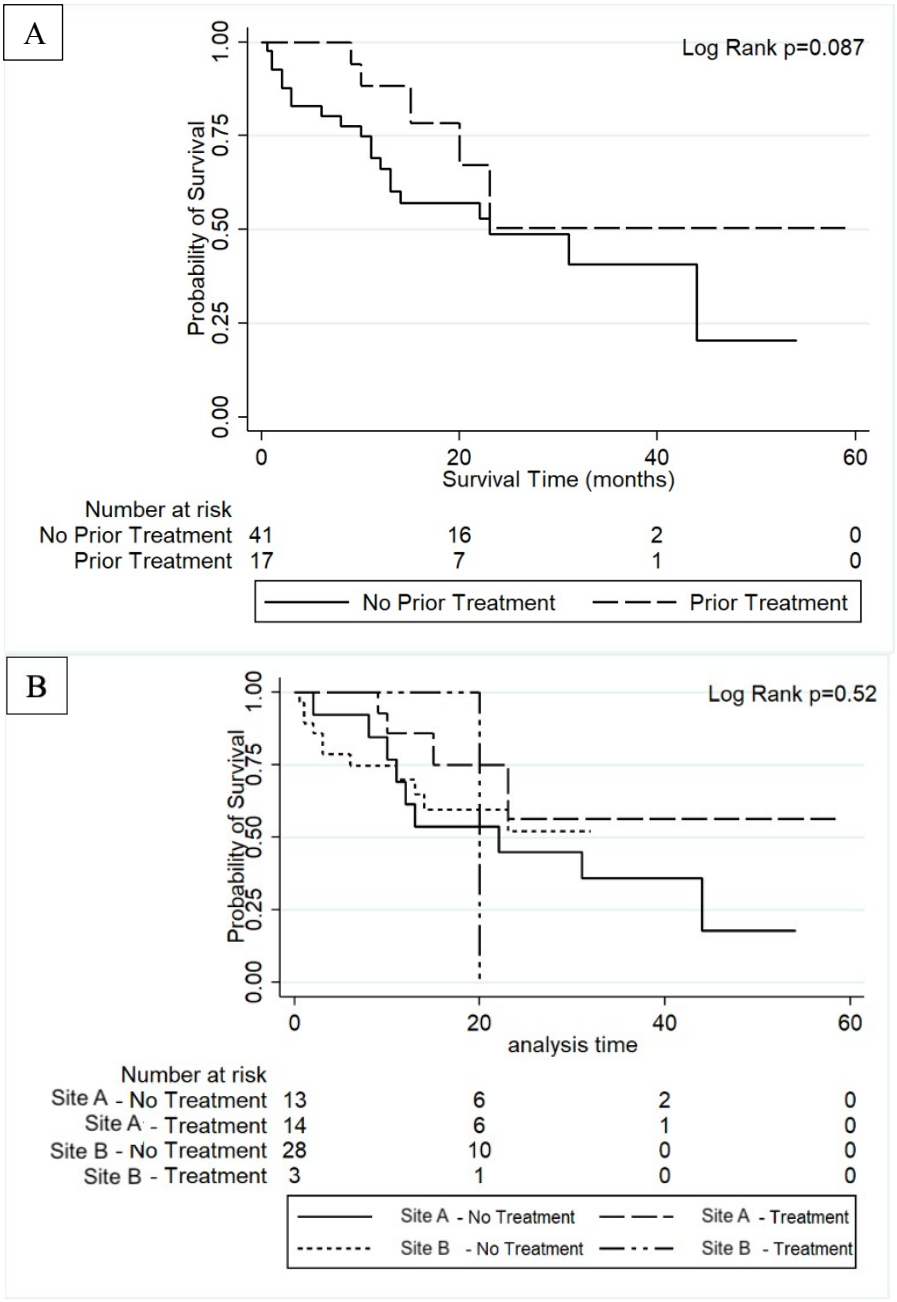

Figure 4. Kaplan-Meier Curve for overall survival. Comparison of overall survival for neoadjuvant therapy vs. no neoadjuvant therapy, both sites combined (A). Comparison of overall survival for Site A (neoadjuvant therapy and no neoadjuvant therapy) vs. Site B (neoadjuvant therapy and no neoadjuvant therapy) (B).