

Clinical Oncology – Hosted by the CT Commission on Cancer

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Neoadjuvant Therapy in Extrahepatic Bile Duct Cancer: Chemotherapy Plus Radiation Outperforms Chemotherapy Alone

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Introduction: Surgical resection with negative margins conveys the highest likelihood of long-term survival for patients with extrahepatic bile duct (EHBD) cancer. While adjuvant systemic therapy is frequently administered, experience with neoadjuvant therapy (NAT) is extremely limited. However, given recent promising results of NAT in pancreatic cancer, there has been increasing interest in neoadjuvant treatment for EHBD cancer. To guide future investigations, this study aimed to compare the outcomes of neoadjuvant chemotherapy (NAC) to neoadjuvant chemotherapy plus radiation (NAC+R) prior to resection of EHBD cancer in a large, national cohort.

Methods: Patients with stage I-III EHBD cancer diagnosed between 2004 and 2017 who underwent either NAC or NAC+R prior to definitive surgical resection were identified using the National Cancer Database (NCDB). Odds of negative resection margin, overall survival, and rate of downstaging in the two groups were compared using multivariable logistic regression, multivariable Cox proportional hazards regression, and Chi-squared analysis, respectively.

Results: Of 14,391 patients with non-metastatic EHBD cholangiocarcinoma or adenocarcinoma, 74 underwent NAC and 61 underwent NAC+R. Those who underwent NAC+R were younger (mean age 57.5 vs. 64.3, $p < 0.001$) and more likely to be diagnosed in an earlier year (mean year 2012 vs. 2014, $p < 0.001$) (Table 1). There was no difference between the groups in baseline Charlson-Deyo comorbidity index ($p = 0.210$) or in clinical stage ($p = 0.433$). The groups did not differ in rate of downstaging ($p = 0.822$). Positive margins were less common in the NAC+R group (5.2% vs. 24.7%, $p = 0.003$). On multivariable logistic regression, NAC+R was associated with higher risk-adjusted odds of a negative surgical margin compared to NAC alone (odds ratio = 8.9, 95% confidence interval 2.1-38.2, $p = 0.003$), although this did not translate to a statistically significant decrease in risk-adjusted mortality rate (hazard ratio for NAC+R = 0.68, 0.40-1.17, $p = 0.161$).

Conclusion: A small number of patients with EHBD cancer have successfully undergone margin-negative resection following NAT, with survival comparable to historical controls. NAC+R is associated with a higher likelihood of margin-negative resection in those patients who reach operation, but there is no clear difference in overall survival compared to those who underwent NAC alone prior to surgery. Future studies should focus on identifying the patients most likely to benefit from NAT and on collecting prospective data to determine the most viable and effective NAT regimens.

	NAC	NAC+R	p-value ^a
n	74	61	-
Age, mean ± SD	64.3 ± 10.7	57.5 ± 14.3	0.002
Sex, % male	57% (42/74)	67% (41/61)	0.214
Year of Diagnosis, mean ± SD	2014 ± 2	2012 ± 3	<0.001
Charlson-Devo Score			
0	72% (53/74)	84% (51/61)	0.210
1	19% (14/74)	7% (4/61)	
2	5% (4/74)	5% (3/61)	
3+	4% (3/74)	5% (3/61)	
Change in Stage			
Same stage	60% (44/74)	61% (37/61)	0.822
Downstaged	20% (15/74)	23% (14/61)	
Upstaged	20% (15/74)	16% (10/61)	
Surgical Margin, % Positive	25% (18/73)	5% (3/58)	0.003

Abbreviations: NAC = neoadjuvant chemotherapy; NAC+R = neoadjuvant chemotherapy plus radiation

Advanced Clinical Stage is Associated with An Increase in Social Vulnerability Index Among Women Undergoing Breast Lumpectomy

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Introduction: Addressing social and economic factors of female patients may aid in timely diagnosis of malignancy, thereby increasing treatment options and most likely overall survival. The Geospatial Research, Analysis, and Services Program (GRASP) developed a quantifiable measure of these barriers by creating the first version of the Social Vulnerability Index in 2011 using census data to identify at-risk groups during crises. The goal of their initiative is to address community needs and prepare for public health emergencies. SVI has also been utilized to understand the social vulnerability of patients to aid in the development of community health initiatives. We sought to understand the SVI of patients undergoing lumpectomy and the effect of initial breast cancer staging.

Method(s): Retrospective review of women undergoing breast lumpectomy for malignancy from over one year was collected within the state health system. The Social Vulnerability Index (SVI) of patients who underwent breast lumpectomy who presented with Clinical Stages 0-3, was considered. The four categories that constitute the SVI including, Socioeconomic Status (S), Household Composition and Disability (H), Minority Status and Language (L) and Housing Type and Transportation (T) were considered. Exclusion criteria included men and those with home addresses outside of Connecticut, or those with only PO boxes due to inability to identify their home address. ANOVA was utilized to compare SVI categories across clinical stages.

Results: All female residents of Connecticut undergoing breast lumpectomy in the year 2022 were included (n=196). Overall, there was a statistically significant difference (p=0.04) in the social vulnerability index trend in patients who presented with CS0 to CS3 with a later stage being associated with a higher SVI. When assessing each of the four components of SVI, Minority Status and Language SVIs was statistically significant between the groups (p= 0.049). The housing and transportation SVIs were nearly significant (p= 0.057).

Conclusions: This study demonstrates the societal differences in patients diagnosed with breast cancer who underwent breast lumpectomy. We show that their social vulnerability differs and that an increased SVI is associated with an advanced clinical stage at diagnosis. This information should be utilized to further develop community programs to reduce this disproportionate burden.
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Clinical Stage	Frequency	Overall SVI	S	H	L	T
0	23	0.43	0.43	0.54	0.39	0.45
1	128	0.47	0.48	0.50	0.45	0.45
2	36	0.6	0.57	0.58	0.56	0.58
3	5	0.58	0.67	0.68	0.57	0.39
	P Value	0.04	0.08	0.25	0.049	0.057

Socioeconomic Status (S), Household Composition and Disability (H), Minority Status and Language (L) and Housing Type and Transportation (T)

Immunotherapy Initiation at the End of Life is Increasing for Metastatic Melanoma Patients

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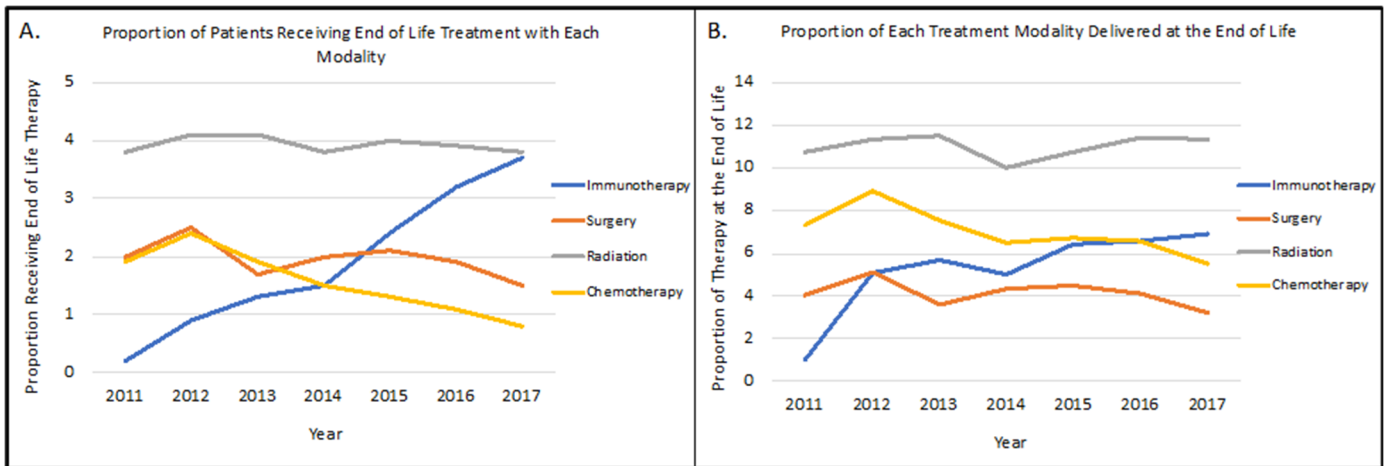
Introduction: Due to its associations with a higher quality end of life (EOL) and decreased healthcare costs, avoidance of chemotherapy at the EOL has been widely recognized as an important quality measure in oncologic care for many years. However, since modern immunotherapeutic agents revolutionized the treatment of metastatic melanoma in 2011, prescribing practices near the EOL for these expensive and sometimes morbid treatments have not been given the same attention. This study examines national trends in EOL immunotherapy for patients with stage IV melanoma and describes the cohort of patients subjected to EOL immunotherapy.

Methods: The National Cancer Database was used to identify patients with stage IV melanoma diagnosed between 2011 and 2017. Initiation of a treatment within one month of death was considered to be EOL treatment. National trends in immunotherapy and in its EOL use were described. Characteristics of the cohort receiving EOL immunotherapy were examined. Factors associated with EOL immunotherapy were identified.

Results: There were 16,652 stage IV melanoma patients in the study. Overall rate of immunotherapy utilization increased from 15% in 2011 to 54% in 2017 ($p < 0.001$ for trend). The proportion of all patients that received EOL immunotherapy has increased steadily from 0.2% in 2011 to 2% in 2014 to 4% in 2017 ($p < 0.001$) (Figure 1A). EOL care represented 7% of all immunotherapy treatments in 2017, up from 5% in 2014 and 1% in 2011 ($p < 0.001$) (Figure 1B). In contrast, the proportion of chemotherapy patients initiating their treatment at the EOL was unchanged over the study time frame ($p > 0.05$). Patients receiving EOL immunotherapy had a mean age of 64.4 years and were predominantly male (73%), from a wealthier zip code (38%), Medicare-insured (52%), and had a Charlson-Deyo comorbidity index of 0 (74%). On risk-adjusted analysis, patients receiving immunotherapy were significantly less likely to receive it at the EOL if they were treated at an academic (OR=0.46, 95% confidence interval = 0.30-0.73, $p = 0.001$) or a network (OR=0.58, 0.35-0.94, $p = 0.027$) facility rather than a community facility, as were patients treated at a high-volume (OR=0.57, 0.43-0.77, $p < 0.001$) rather than low-volume center. In 2017, 16% of patients receiving immunotherapy at a community facility received it at the EOL, compared to 6% of patients treated at an academic facility ($p = 0.002$). Palliative care was more commonly utilized in those that received EOL immunotherapy than in those that did not (28% vs. 15%, $p < 0.001$). Immunotherapy patients were more likely to initiate immunotherapy at the EOL if they had liver-only metastases (OR=7.41, 2.23-24.62, $p < 0.001$) or two solid organ metastatic sites (OR=9.95, 3.59-27.63, $p = 0.001$) rather than lung-only metastases.

Conclusions: The share of metastatic melanoma patients that are started on immunotherapy within one month of death is increasing significantly. Treatment at a community or low-volume facility is a risk factor for receipt of EOL immunotherapy. These findings suggest that there may be an opportunity for more judicious prescribing of immunotherapy in the sickest melanoma patients.

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Duodenal Intussusception Secondary to Hamartomatous Polyps of the Duodenum and a Review of the Literature

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Introduction: Hamartomas of the duodenum are benign duodenal tumors comprising approximately 5-10% of duodenal tumors. The incidence is <0.01%. Typically asymptomatic, they may manifest as intestinal obstruction, gastrointestinal hemorrhage, biliary obstruction or intussusception. Intussusception as a manifestation of duodenal hamartoma is rare in itself with less than 200 cases reported in the literature.

Methods: A systemic literature review was performed encompassing all cases presenting with symptomatic intussusception secondary to a hamartomatous polyp of the duodenum. Etiology of symptomatic intussusception included gastrointestinal hemorrhage, gastric outlet obstruction, gastrointestinal hemorrhage with concurrent gastric outlet obstruction and biliary obstruction. Treatments for each presenting etiology were explored.

Results: 17 cases of duodenal intussusception secondary to a hamartomatous polyp were identified. Two presented with gastrointestinal bleed (GIB), seven with gastric outlet obstruction (GOO), five with a combination of the two and only three with biliary obstruction. Only one case was successfully treated with endoscopic polypectomy. Most were achieved by local excision (47%) followed by segmental bowel resection (SBR) (24%). Two cases underwent resection with Billroth II reconstruction and one resected with a Roux en Y gastrojejunostomy. Only one case underwent a pancreaticoduodenectomy.

Conclusion: Duodenal hamartomas are indeed a rare entity and typically asymptomatic. Even rarer are hamartomas resulting in symptomatic intussusception. Complications from these intussusceptions are far from few with only 17 described in the literature. Curative management can be achieved with less invasive methods such as local resection as almost half of presenting cases were treated this way avoiding more morbid measures such as gastrointestinal reconstruction and pancreaticoduodenectomy.

Patient Presentation and Intervention Performed

	Endoscopic Polypectomy	Local Excision	SBR	Whipple	Roux-en-Y Reconstruction	Unknown	Frequency of Symptom
GIB	0	1	1	0	0	0	2 (12%)
GOO	0	4	1	1	1	0	7 (41%)
GIB + GOO	1	1	2	0	1	0	5 (29%)
Biliary Obstruction	0	2	0	0	0	1	3 (18%)
Frequency of Intervention	1 (6%)	8 (47%)	4 (24%)	1 (6%)	2 (12%)	1 (6%)	17

Liver Resection for Metastatic GIST Tumor Improves Survival in the Era of Imatinib: A Systematic Review and Meta-Analysis

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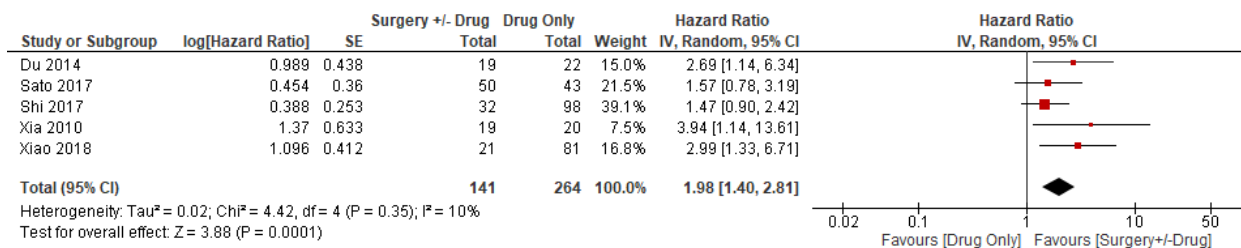
Introduction: Survival for gastrointestinal stromal tumor (GIST) has been increasing over the years with the introduction of tyrosine kinase inhibitors. However, the role of metastasectomy for GIST is still controversial. Patients are currently treated with imatinib or sunitinib in case of imatinib failures as optimal medical therapy.

Methods: The Pubmed, EMBASE, and Cochrane Library were systematically searched. Overall survival following liver resection +/- tyrosine kinase inhibitor treatment for metastatic GIST were compared with treatment with tyrosine kinase inhibitors alone.

Results: Five studies including a total of 405 patients (141 surgery +/- drug group and 264 drug only group) were included. Overall survival was significantly improved in patients undergoing liver resection +/- drug therapy in comparison to drug therapy alone. [HR (95%CI) = 1.98 (1.40, 2.81); p=0.0001]. Subgroup analysis showed that patients also had improved progression free survival based on 3 studies. [HR (95%CI) = 1.79 (1.30, 2.46); p=0.0004]. In case of concurrent liver and peritoneal metastases, patients showed improved overall survival with aggressive surgical approaches based on 8 studies. [HR (95%CI) = 1.83 (1.48, 2.26); p<0.00001].

Conclusion: This meta-analysis found that liver resection for patients with metastatic GIST regardless of peritoneal metastases improved progression free and overall survival in conjunction with tyrosine kinase inhibitors as compared with medical therapy alone. Furthermore, liver resections did not have any immediate detrimental impact on survival in the group of patients selected.

Overall Survival: Liver resection + medical therapy vs medical therapy for metastatic GIST



Neoadjuvant Chemotherapy Achieves Pathologic Complete Response in a Patient with Stage IV Colon Cancer - A Case Study

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Introduction: Colorectal cancer is the third most common cancer in males and females in the United States. Neoadjuvant chemoradiotherapy with or without chemotherapy is the standard of care for locally advanced rectal cancer, however there is no consensus on which patients with colon cancer should receive neoadjuvant therapies rather than upfront surgery. Historically, patients who are deemed appropriate for initial chemotherapy are those with locally unresectable colon cancer, those who are poor surgical candidates, or those whose margins of resection could potentially be compromised.

Case studies have shown instances of pathologic complete response (PCR) after neoadjuvant chemotherapy in patients with locally advanced colon cancer. This case study presents one patient with stage IV colon cancer with liver metastases who achieved PCR after neoadjuvant chemotherapy followed by surgical resection. The purpose of this case study is to contribute to the literature to determine the role for neoadjuvant chemotherapy instead of upfront surgical resection in patients with colon cancer.

Methods: This case study is based on a single patient from a single institution. Data is gathered via retrospective chart review.

Results: A 52-year-old Caucasian male was diagnosed with moderately differentiated sigmoid colon cancer during a routine screening colonoscopy. The tumor showed intact expression for all mismatch repair proteins and no mutations were detected in

KRAS, NRAS, or BRAF. PET CT scan revealed three hypermetabolic lesions in the left lobe of the liver that was confirmed to be metastatic adenocarcinoma consistent with colorectal primary on biopsy. After discussion at the multidisciplinary tumor board, the patient underwent nine cycles of neoadjuvant chemotherapy with Folfox and Avastin which he tolerated with minimal side effects. He then underwent a laparoscopic left liver hepatectomy with final pathology showing PCR. Three months later he then underwent a robotic assisted low anterior resection and liver lesion biopsy with final pathology also revealing PCR.

Conclusions: Pathological complete response has been observed in a patient with stage IV colon cancer after neoadjuvant chemotherapy followed by surgical resection. This shows the benefits of neoadjuvant chemotherapy instead of upfront surgery in select patients. Further research is warranted to determine the role for neoadjuvant chemotherapy for locally advanced colon cancer and to determine whether neoadjuvant chemotherapy may eliminate the need for surgical resection in these patients who demonstrate pathologic complete response.

Radiographic Identification of Positive Clipped Node in Surgical Specimen Following Neoadjuvant Chemotherapy

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Introduction: The emergence of sentinel lymph node biopsies has allowed for the avoidance of axillary lymph node dissection in many patients with biopsy-proven, node-positive breast cancer, who have responded to neoadjuvant chemotherapy (NAC). Current guidelines support the omission of an axillary lymph node dissection in patients who have at least three negative sentinel lymph nodes retrieved during surgery. Consequently, the utility of routine clip placement in biopsied lymph nodes prior to patients undergoing NAC and necessity of subsequent targeted removal of these clipped nodes has been widely debated. We describe a case in which intraoperative specimen radiograph identified the clipped node which had not been identified with targeted axillary dissection and the impact the pathology findings had on subsequent management.

Method(s): A 43-year-old BRCA1 gene-positive female with biopsy-proven ER+/PR-/Her2- stage IIB (T2N1M0) left breast invasive ductal carcinoma underwent NAC with radiologically proven partial response. She elected to undergo bilateral total mastectomies with left sentinel lymph node biopsy and targeted axillary dissection. Technetium 99 sulfur colloid was injected the night before surgery and methylene blue dye was injected intraoperatively for localization of axillary sentinel lymph nodes. During the procedure, three negative sentinel left axillary lymph nodes were retrieved, but the localizing clip was not identified on intraoperative X-ray. The left breast mastectomy specimen with axillary tail was then examined ex-vivo under X-ray, with identification of the clipped lymph node and subsequent excision during back table dissection.

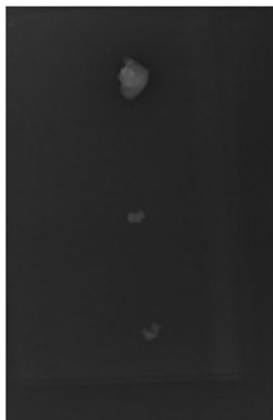


Figure 1. Sentinel Lymph Nodes.
Radiograph of three axillary sentinel lymph nodes from dissection. Negative for metastatic disease.

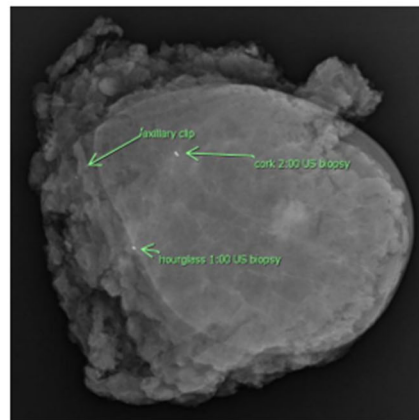


Figure 2. Surgical Mastectomy Specimen.
Radiograph of excised left breast specimen containing clipped axillary node. Positive for metastatic disease.

Results: The clipped node was found to be involved with metastatic disease, and therefore an axillary lymph node dissection was performed. Metastatic carcinoma was identified in four out of twenty axillary lymph nodes. As a result of her significant residual

burden of disease, the patient received comprehensive post-mastectomy radiation therapy to the chest wall, axilla, and supraclavicular fields. Also, in addition to adjuvant tamoxifen, she was placed on Zoladex and Olaparib.

Conclusion(s): This case demonstrates the utility of clipped node localization via intraoperative imaging of the mastectomy specimen in a patient in whom there was difficulty identifying the clipped node. Despite the assertion by some authors that failure to retrieve the clipped node does not affect post-surgery treatment, in our patient it resulted in appropriate escalation of her subsequent treatment. We advocate for the routine use of specimen imaging for clip localization during targeted axillary dissection.

Effect of Interruption of Thromboembolic Prophylaxis on Development of Thrombotic Complications Following Distal Pancreatectomy

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Introduction: Venothromboembolic (VTE) prophylaxis is indicated for surgical patients with pancreatic cancer as there is a significant risk of developing a deep vein thrombosis (DVT) post-operatively. The data for when to initiate VTE prophylaxis after pancreatic surgery is inconclusive and support for preoperative chemoprophylaxis is limited since the risk of hemorrhage often exceeds that of thrombosis making it difficult to standardize a regimen. At this institution, distal pancreatectomies routinely receive subcutaneous heparin 5000 units every 8 hours or subcutaneous enoxaparin 40 mg once daily pre-operatively and/or post-operatively. The purpose of this study was to determine the cause and impact of missed dosing peri-operatively in distal pancreatectomy patients.

Methods: A retrospective, cohort, single-center study was performed comparing the development of thrombotic complications following pancreatectomies in patients who experienced interruptions in thromboembolic prophylaxis to patients who had no interruptions in their prophylactic regimen. The inclusion criteria consisted of the following: ages 18-80, any gender, date of operation 1/2018-1/2022, and distal pancreatectomy performed at this institution. Any patient that died within 24 hours of surgery was excluded from the study. Outcomes were compared between patients who missed VTE prophylactic doses and those who did not post-operatively. For subgroup comparison, categorical data was compared with chi-square tests or Fisher's exact tests when the sample size was small; continuous data that did not meet the normality assumption were tested with Mann-Whitney U tests.

Results: A total of 51 patients that met the inclusion criteria were identified between January 2018 and January 2022. Of the 51 patients, 24 patients did not have any disruption in VTE prophylaxis [adherence group] and 27 patients had ≥ 1 disruption (24 patients with 1 missed dose) in VTE prophylaxis during hospitalization [non-adherence group]. Patients in both of the groups had similar characteristics (age, gender, race, BMI, insurance, obesity, smoking history), comorbidities, and other medical conditions. However, a higher proportion of patients in the non-adherent group had a previous abdominal surgery (88.9% vs 58.3%, $p=0.012$) and were administered epidurals (88.9% vs. 37.5%, $p<0.001$). Postoperatively, there was no difference in time to initiate first VTE prophylactic dose with a median time of 5.2 hours (IQR 3.2-10.2hr). Additionally, there was no differences in rate of VTE development, infection, or death between both groups within 90 days of surgery. Only one patient developed a DVT in this study. The main reasons for interruption of VTE prophylaxis were epidural removal (61.3%), prescription order issue (29.0%), and bleeding (6.5%). The total proportion of missed doses among the non-adherence group was 7.4%.

Conclusions: Prior studies demonstrate a VTE rate as high as 40% in patients with pancreatic cancer. The adherence and non-adherence groups had similar VTE rates with only one patient in the non-adherent group developing a DVT. VTE prophylaxis administration pre-operatively (58.8%) and intra-operatively (23.5%) with continuation or initiation promptly after surgery could have contributed to the low VTE rate. Limiting the interruption of VTE prophylaxis post-operatively may have also contributed to the low rate as most non-adherent patients missed only one dose. The most common reasons for interruption were the removal of an epidural catheter and prescription ordering. The rate of missed dosing points to improving coordination of epidural removal with administration of VTE prophylaxis. However, this limited interruption does not appear to increase the DVT rate. Even though this

study did not show a difference in the development of VTE, the study itself is limited by its small sample size. Future studies with a larger sample size are needed to support and further this analysis.

Patient Demographics & Clinical Characteristics of Adult Inpatient Admissions for Malignant Melanoma

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Introduction: The annual incidence of malignant melanoma in the U.S. increases yearly. Most patients with melanoma receive definitive care in outpatient settings; however, some patients are admitted to inpatient care. We sought to identify factors associated with hospital admission and quantify sex-based differences in treatment and outcomes among adults admitted to inpatient care in the U.S. with a primary diagnosis malignant melanoma.

Methods: Using data from the HCUP National Inpatient Sample from 2016-2019, ICD-10-CM diagnosis codes identified patient admissions with a primary diagnosis of malignant melanoma. Records were excluded if patient age was <18 or sex was missing. Data were weighted to represent the national population and admission characteristics; treatment and outcomes were examined by sex. Chi-square tests and weighted bivariable quantile regression compared categorical and continuous variables, respectively.

Results: A total of 8,175 admissions met criteria, representing 5.7/100,000 admissions nationwide. The majority (63.7%) of patients were male. Median age did not differ (females: 68; males 67; $p=0.335$), although there were significant differences in categorical age distribution, with proportionally more females in the age groups under 60 or ≥ 80 than males ($p<0.001$) while males were more often in the 60-69- and 70-79-year age groups. Primary lesions of the head/neck/face region were most common among males and less common among than females (35.5% vs. 17.7% respectively [$p<0.001$]). The most common primary location for females was the lower limb area, which was less common among males (38.8% vs. 17.9%, respectively [$p<0.001$]) A total of 6,685 (81.8%) patients has at least one surgical procedure (see below). Median admission cost was \$10,832 (IQR \$6,616-\$17,209) for females and \$11,797 (IQR \$7,364-\$18,881) for males ($p=0.04$). Routine discharge was less likely among females than males (53.5% vs. 61.0%, respectively; $p=0.007$). Half of admissions for both sexes included a diagnosis of secondary malignancy; 11% of patients with secondary malignancy died during admission vs. 1.2% of those without ($p<0.001$).

Conclusion: Substantial between-sex variability in demographic and clinical characteristics was observed. Importantly, admission with secondary malignancy was associated with a near 10-fold increase in proportional mortality during the index hospitalization. Further understanding sex-based differences in characteristics of inpatient admission and treatment of malignant melanoma may support future optimization of sex-specific prevention screening/observation strategies.

Table 1: Most common procedures performed by category* during inpatient admission with a primary | diagnosis of malignant melanoma (N=2,455 female and 4,230 male patients undergoing surgery)

Procedure category	Female N (%)	Male N (%)	Total N (%)	p-value
Skin graft	770 (31.4)	1,385 (32.7)	2,155 (32.2)	0.599
Skin excision and debridement	750 (30.5)	1,250 (29.6)	2,000 (29.9)	0.689
Lymph node biopsy	790 (32.2)	1,160 (27.4)	1,950 (29.2)	0.057
Subcutaneous tissue and fascia excision	670 (27.3)	965 (22.8)	1,635 (24.5)	0.071
Lymph node dissection	270 (11.0)	1,125 (26.6)	1,395 (20.9)	<0.001
Salivary gland excision	110 (4.5)	555 (13.1)	665 (9.9)	<0.001
Subcutaneous tissue and fascia procedures, NEC	190 (7.7)	460 (10.9)	650 (9.7)	0.066
Skin biopsy and diagnostic drainage	165 (6.7)	335 (7.9)	500 (7.5)	0.414
Lymph node excision (therapeutic)	200 (8.1)	300 (7.1)	500 (7.5)	0.471

Note: multiple procedures were performed for some patients

*Categories defined by the Healthcare Cost and Utilization Project Clinical Classifications Software-Refined based on ICD-10-PCS codes