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P-9 Gallbladder cancer in the United States: Identifying factors associated with failure to treat

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Background: Adjuvant chemotherapy (AC) should be considered for all patients with surgically resected T1b-T3, high-risk (node-positive) gallbladder cancer (GBC). However, in the United States, few patients receive AC. We sought to identify physician- and patient-specific factors associated with and reasons for low AC use for high-risk T1b-T3 GBC.

Methods: We performed a retrospective review of the National Cancer Database from 2004-2017, identifying patients with T1b-T3 GBC who underwent surgical resection. Exclusion criteria were non-surgical management; death within 60 days of definitive surgery; T1a, T4, or metastatic disease; and receipt of neoadjuvant therapy. To identify a cohort in which all patients should be candidates for AC, our analysis focused on patients with T1b-T3, node-positive disease. Receipt or recommendation of AC within 90 days of definitive surgical procedure was described; for patients for whom AC was not recommended or received, the reason was noted. Trends in AC recommendation rate were evaluated using the Cochrane-Armitage test. Five-year overall survival (OS) by lymph node status and AC receipt were described with Kaplan-Meier and Cox proportional hazards modeling.

Results: 2,765 patients with T1b-T3 GBC met study criteria. Of these, 30% (n=832) had positive lymph nodes and 27% (n=755) had positive resection margins. Most were older than 65 years of age (61%), non-Hispanic White (65%), female (70%), and had a Charlson Comorbidity Index of 0 (70%). Of those with positive lymph nodes, 53% (n=436) were recommended and received AC, 31% (n=254) were not recommended AC because "chemotherapy is not indicated for this condition," 4% (n=32) were not recommended AC due to patient risk factors, and 14% (n=110) did not receive recommended AC due to patient death, patient refusal, or unknown reason. Rate of AC recommendation for patients with node-positive disease significantly increased throughout the study period, from 58% in 2004 to 71% in 2017 (p£0.05). Odds of AC recommendation for node-positive patients were increased in the more recent time frame (2012-2017 vs 2004-2011; OR 1.79, CI 1.33-2.41) and for younger patients (ages 18-64 vs 55-64; OR 1.83, CI 1.3-2.58), but decreased with age >65 (vs 55-64; OR 0.46, CI 0.32-0.68). While the 5-year OS of node-positive patients who did not receive CT was 17% throughout the study period, the 5-year OS of node-positive patients who received CT was prolonged in the more recent time period: from 20% in 2004-2011 to 28% in 2012-2017 (p=0.06).

Conclusions: For patients with node-positive T1b-T3 GBC, AC recommendation rate increased over time, and was associated with prolonged OS. However, low AC use was most frequently related to the physician perception that "chemotherapy is not indicated." In contrast, poor performance status and patient refusal were only rarely responsible for low AC use. Our data suggest that physician-dependent factors are the predominant driver of failure to treat patients with high-risk GBC - namely, that physicians believe AC is not indicated for these patients. Improving physician education is likely key to improving AC rates and survival outcomes for patients with node-positive T1b-T3 GBC.

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P-10 Standardization of a neoadjuvant therapy (NAT) pathway for pancreatic cancer across a geographically large and diverse healthcare system improves patient care and successful completion of NAT

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Background: Optimal management of patients with potentially resectable pancreatic ductal adenocarcinoma (PDAC) is controversial and variation exists within/across academic and healthcare systems. Herein we describe the initial results of a neoadjuvant therapy (NAT) pathway across one of New York's largest, most diverse health care systems.

Methods: The NAT pathway was established at Northwell Health in June 2019, consisting of an initial, single-day pancreas multi-disciplinary clinic (PMDC) visit, followed by NAT, interval scans and PMDC re-reviews at two and four months, prior to consideration of radiation and of surgical resection. We conducted an IRB-approved retrospective analysis of patients enrolled to this pathway. Primary endpoints included completion of NAT pathway and overall survival (OS). Kaplan-Meier analysis was used to estimate OS.

Results: The cohort consisted of 55 patients: 44% men, mean age 69.7 years, and 48% non-White. Surgical stage at diagnosis was locally advanced (LAPC; 49%), borderline resectable (BRPC; 35%) and resectable (RPC; 16%). NAT consisted of gemcitabine/nab-paclitaxel (GnP, 41%; 147 total cycles), FOLFIRINOX (36%; 167 total cycles), and a combination of both regimens (23%). Eighteen (33%) received radiotherapy (94%, SBRT) and 72% received >=50 Gy. Average duration of NAT pathway (from biopsy to surgery) was 5.9 mo (IQR 4.7-7.6 mo): average time from biopsy to C1 of NAT was 25 days (IQR 18-39 days), from C1 to post NAT completion imaging was 3.9 mo (IQR 3.5-4.8 mo) and from RT to surgery was 36.0 days (IQR 30.5-43.8 days). Of 55 patients who began the pathway, 24 (44%; 6% RPC, 53% BRPC, 41% LAPC) completed the pathway and underwent surgical exploration; 22 did not complete the pathway and 9 are currently undergoing NAT. Reasons for not completing NAT included metastasis (24%), transfer of care (12%), local progression (5.5%), and death (3.6%). Out of 24 patients who were surgically explored, 71% underwent successful resection (53% R0, 18% R1 < 1mm and 30% R1) compared to prior institutional resection rate in NAT patients of 17% (p=0.015). There were 11 deaths (20%) and median OS was reached at 17.7 mo (95% CI 7.9, 27.6): 16.3 mo 95% CI 7.2, 25.4) and 26.1 mo (95% CI 3.2, 49) for GnP and FOLFIRINOX, respectively. Patients enrolled in the NAT pathway had a higher rate of germline mutation testing (52% vs 30%, p=0.002). The percentage of patients that remained within the Northwell Health system for their post-NAT was higher among patients in the pathway, compared to prior (87% versus 44%).

Conclusions: Implementation of a standardized NAT approach at a large diverse healthcare system increased the percentage of PDAC patients who underwent surgical resection and improved patient retention rate. Our data lay the groundwork for further studies that will provide long term outcomes of NAT in these patients.

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P-11 Venous thromboembolism in colorectal cancer patients with BRAF mutation

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Background: Venous thromboembolism (VTE) is a frequent complication in colorectal cancer (CRC) patients. In these patients, some molecular biomarkers, such as KRAS mutation, have been associated with an increased risk of thrombosis. However, little is known about the characteristics of VTE associated with less prevalent molecular biomarkers. The aim of this analysis is to describe the characteristics of VTE of a cohort of ambulatory CRC patients harboring BRAF mutation.

Methods: We performed a retrospective review of consecutive patients with BRAF-mutated CRC attended in the Medical Oncology Department of 10 hospitals from the network of the Cancer & Thrombosis Section of the Spanish Society of Medical Oncology (SEOM). Between January 2014 and June 2018, 165 patients were identified and included in the analysis.

Results: Mean age was 63.47 years (standard deviation [SD] 11.50 years) and 46.7% (n=77) were men. With a median follow-up of 15 months (interquartile range [IQR] 9-25), forty patients (24.2%) developed a VTE (32.4% pulmonary embolism, 24.3% lower-extremity deep-vein thrombosis [DVT], 2.7% upper-extremity DVT, 16.2% visceral thrombosis, 18.9% catheter related-thrombosis, 5.4% others). Most patients had metastatic disease (90.0%) and was receiving systemic therapy (73.7%). Median time from CRC diagnosis to VTE was 5.06 months (IQR 2.85-10.81). 50.0% of events were diagnosed incidentally and 75.0% in the ambulatory setting. Most patients (87.5%) received anticoagulant treatment (low-molecular-weight heparins [LMWH] 33 patients, direct oral anticoagulants [DOACs] 1 patient, others 1 patient), 35.9% for more than 6 months. 6 patients (15.4%) experienced VTE recurrence and 7 patients

(19.4%) bleeding (mayor or fatal bleeding 4 patients). Median survival was 20.86 months for non-VTE patients and 11.30 months for VTE patients (hazard-ratio [HR] 2.13; CI 95% 1.38-3.28; p=0.001).

Conclusions: VTE is associated with increased morbidity and mortality in patients with BRAF-mutated CRC.

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P-12 A phase 3 study of nivolumab (NIVO), NIVO + ipilimumab (IPI), or chemotherapy for microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC): CheckMate 8HW

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Background: Patients with MSI-H/dMMR mCRC treated with chemotherapy have poorer outcomes than patients with microsatellite stable/MMR proficient mCRC. Pembrolizumab monotherapy is approved in multiple countries as first-line therapy for patients with MSI-H/dMMR mCRC; however, despite observed clinical benefit vs chemotherapy, the 24-month progression-free survival (PFS) rate was 48% (Andre et al. NEJM 2020). NIVO (anti−programmed death 1 [PD-1]) and IPI (anti−cytotoxic T lymphocyte antigen-4 [CTLA-4]) are immune checkpoint inhibitors with distinct but complementary mechanisms. NIVO±IPI is approved in previously treated patients with MSI-H/dMMR mCRC in the US, EU, and Japan, based on findings from the phase 2, non-randomized, multicohort CheckMate 142 study. Indirect comparisons suggest that NIVO (3 mg/kg) + IPI (1 mg/kg) provides improved clinical benefit vs NIVO (investigator-assessed [INV] objective response rate [ORR] 55% vs 31%; 12-month INV PFS rate 71% vs 50%; 12-month overall survival [OS] rate 85% vs 73%) with a favorable benefit-risk profile for previously treated MSI-H/dMMR mCRC (Overman et al. JCO 2018). NIVO+IPI also demonstrated robust and durable clinical benefit and was well tolerated for the first-line treatment of MSI-H/dMMR mCRC (INV ORR 69%; 24-month INV PFS rate 74%; 24-month OS rate 79%; Lenz et al. JCO 2022). To date, no prospective phase 3 studies have reported results for anti−PD-1 + anti−CTLA-4 vs chemotherapy or anti−PD-1/programmed death ligand 1 (PD-L1) monotherapy in MSI-H/dMMR mCRC. CheckMate 8HW (NCT04008030) is an international, multicenter, open-label, randomized, phase 3 study designed to compare the efficacy and safety of NIVO+IPI to chemotherapy or NIVO in patients with MSI-H/dMMR mCRC.

Trial design: Approximately 748 patients across 23 countries aged ≥18 years with histologically confirmed recurrent or mCRC that is not amenable to surgery, irrespective of prior treatment with chemotherapy and/or targeted agents, with known tumor MSI-H or dMMR status and ECOG performance status ≤1 will be randomized to receive NIVO, NIVO+IPI, or investigator's choice chemotherapy (patients in the chemotherapy arm can receive NIVO+IPI upon progression). The dual primary endpoints are PFS, assessed by blinded independent central review (BICR), for NIVO+IPI vs NIVO across all lines and NIVO+IPI vs chemotherapy in the first-line setting in patients with centrally confirmed MSI-H/dMMR mCRC. Other key endpoints include PFS by BICR for NIVO+IPI vs NIVO in the first-line setting, PFS by INV, ORR by BICR, OS, and safety. Recruitment of patients in the first-line setting is ongoing.

Clinical trial identification: NCT04008030.

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P-14 Safety and short-term efficacy of preoperative FOLFOX therapy for patients with resectable esophageal squamous cell carcinoma who are not candidates for cisplatin

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Background: The standard treatment for resectable locally advanced esophageal squamous cell cancer (LAESCC) in Japan is a preoperative cisplatin (CDDP)-containing chemotherapy followed by surgery. However, patients with renal or cardiac dysfunction and elderly patients are not candidates for CDDP because of renal toxicity and the need to ensure adequate hydration. Oxaliplatin, 5-fluorouracil, and leucovorin (FOLFOX) therapy, which causes less renal toxicity than CDDP-containing regimens and does not require hydration, has efficacy comparable with that of CDDP plus 5-fluorouracil as part of definitive chemoradiotherapy or palliative chemotherapy. However, data on the safety and efficacy of preoperative FOLFOX therapy in patients who are unsuitable for CDDP remains unknown.

Methods: Patients who received preoperative FOLFOX therapy at our hospital between 2019 and 2021 were enrolled in this retrospective study. The main selection criteria were as follows: histologically proven squamous cell carcinoma; cT1N1-3M0, cT2-3N0-3M0, cT1-3N0-3M1, or M1 disease limited to supraclavicular lymph node metastasis (UICC TNM 8th edition); age ≥75 years or renal dysfunction (creatinine clearance < 60 mL/min) or cardiac dysfunction (ejection fraction ≤45% on cardiac ultrasound, past history of heart failure, ischemic heart disease, or poorly controlled arrhythmia); and no history of therapy for esophageal cancer. Preoperative FOLFOX therapy (oxaliplatin 85 mg/m2, leucovorin 200 mg/m2, and 5-fluorouracil 400 mg/m2 [bolus] plus 2400 mg/m2 [continuous] every 2 weeks) was administered for 3 or 4 courses. We evaluated adverse events during preoperative chemotherapy (CTCAE version 5.0) and the relative dose intensity, complete resection rate, and histopathological response.

Results: Thirty-five patients were eligible for inclusion in the study (median age 77 years [range, 65−89]; performance status 0/1, 40%/60%; clinical stage I/II/III/IVB, 11%/29%/57%/3%). The reasons for selecting FOLFOX were renal dysfunction (74%), age ≥75 years (69%), and cardiac dysfunction (17%). The median creatinine clearance in patients with renal dysfunction was 45.0 mg/dL (range, 26.4−56.1). Four patients (11.4%) discontinued chemotherapy because of progression (n=2), febrile neutropenia (n=1), or neutropenia (n=1). The relative dose intensity was 78.9% for 5-fluorouracil and 85.2% for oxaliplatin. The most common grade ≥3 adverse events were neutropenia (60%) and leucopenia (29%). Two patients (6%) developed febrile neutropenia and pneumonia. Granulocyte colony-stimulating factor was used as secondary prophylaxis in 9 patients (26%). Grade ≥3 loss of appetite and nausea were observed in only 1 patient (3%). Mild elevation of creatinine was seen in 2 patients (6%). Of the 35 patients, 4 did not proceed to surgery (patient declined, n=3; pneumonia, n=1). Finally, 31 patients underwent surgery. The complete resection rate was 87% (27/31) and the pathological complete resection rate was 16% (5/31). There were no treatment-related deaths.

Conclusions: Preoperative FOLFOX therapy was well tolerated and showed promising short-term efficacy in patients with resectable LAESCC who were not candidates for CDDP.

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