Ann Surg Oncol (2022) 29:5355–5356
https://doi.org/10.1245/s10434-022-11985-4

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – HEPATOBILIARY TUMORS

Can We Predict Surgical Futility/Cure in Gallbladder Cancer?

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The surgical management of gallbladder cancer is challenging as it requires stratifying the risk of early recurrence with an appreciation of the recurrence patterns characterizing this malignancy. Although National Comprehensive Cancer Network (NCCN) guidelines recommend resection of locoregional sites at risk of harboring residual disease such as segments IVB and V, portal lymphadenectomy and extended hepatic or biliary resection as necessary to obtain a negative margin, the decision to perform surgery is too often tempered by early and frequent distant recurrences, the most common site of surgical failure. High-risk patients may benefit from neoadjuvant chemotherapy before reresection to improve patient selection and avoid the potential morbidity of a nontherapeutic resection. However, this is controversial as a recently published systematic review of six retrospective studies including 420 patients reported that 30% of patients progressed on neoadjuvant chemotherapy and only 157 (37%) subsequently underwent an R0 resection.[1]

In what is one of the largest single-institutional studies, Shimizu et al. analyzed 139 patients with gallbladder cancer for preoperative factors associated with early recurrence (within 6 months of surgery).[2] They identified preoperative CA 19-9 $\geq$ 200, low muscle attenuation, high visceral fat attenuation, and liver and/or other organ invasion as independent risk factors for early recurrence.

CA 19-9 is well established as a prognostic factor in gallbladder cancer, but the cutoff threshold has been variable.[3–6] Furthermore, falsely elevated CA 19-9 can occur in the setting of obstructive jaundice, and false-negative CA 19-9 results occur in patients who are negative for the Lewis blood group phenotype. While body composition is not widely available, automated reporting of low muscle attenuation, high visceral fat attenuation on preoperative imaging may improve the feasibility of the incorporation of body composition analysis into clinical decision-making. Body composition is being increasingly recognized as an important factor in both postoperative morbidity as well as cancer survival, making it an ideal discriminating variable for clinical decision-making.[7,8]

The authors utilized these prognostic factors to create a nomogram with excellent discrimination (AUC 0.881) to predict early postoperative recurrence. Unfortunately, because of the limited sample size, they were unable to form a training and validation set and have not yet performed external validation, so the model remains unvalidated. Preoperative predictive nomograms are commonly published but rarely used clinically due to the difficulty of obtaining all preoperative factors, the use of subjective or inaccurate measurements, the difficulty in calculating the score, and lack of utility in altering the management of patients. Although the current study has several of these limitations, its strength lies in the excellent discrimination and the highly relevant clinical endpoint of early postoperative recurrence, which may make it clinically useful. For example, neoadjuvant chemotherapy is currently a category 2B consideration for resectable gallbladder cancer. Figure 4 illustrates that patients with 0–3 points were at low (1.9%) risk of early recurrence, with 103 (74%) of patients falling into this category. The median OS for those without early recurrence was 104.7 months, suggesting that these patients may not need perioperative chemotherapy. If validated, this is a large subgroup who could be potentially spared the toxicity of neoadjuvant chemotherapy. In contrast, patients with a score of 6–8 had seven (78%) early recurrences, which was associated with a median OS of 15.7 months, similar to the median OS of the cohort who had aborted resections due to metastatic

First Received: 24 May 2022
Accepted: 25 May 2022
Published Online: 7 June 2022

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disease, suggesting that these high-risk patients may not benefit from attempted surgical resection and, if validated, could be potentially spared the morbidity of a futile resection. The 27 (19%) patients with a score of 4–5 had an intermediate risk of early recurrence and may be the ideal group who would benefit from neoadjuvant systemic chemotherapy to identify responders and nonresponders for improved patient selection.

The nomogram may also be applied to the selection of patients for multivisceral resection. Although the authors of the current study did not report their postoperative morbidity and mortality, a recent review of the Netherlands Cancer Registry reported significant (57% had grade $\geq$ 3A) morbidity and mortality (12% 90-day mortality) for patients undergoing major hepatectomy or pancreaticoduodenectomy as part of an extended resection of gallbladder cancer. They also reported a median OS of only 12 months but long term (5-year) survival in a small (15%) subset of patients.[9] Thus, application of a clinical nomogram such as the one proposed by the authors could be utilized to select out patients at high risk of early recurrence after extended resection.

As with any nomogram, external validation in diverse patient clinical and demographic groups as well as evaluation of the optimal cutoff thresholds for each factor are necessary to strengthen the clinical utility of this nomogram.

DISCLOSURES The author has nothing to disclose.

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