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EDITORIAL – REGIONAL CANCER THERAPIES

Regional Therapies for Cancer

T. Clark Gamblin, MD, MS[1], H. Richard Alexander, MD[2], Robert Edwards, MD[3], and David L. Bartlett, MD[4]

[1]Division of Surgical Oncology, Department of Surgery, Medical College of Wisconsin, Milwaukee, WI; [2]Department of Surgery, University of Maryland, Baltimore, MD; [3]Division of Gynecologic Oncology, University of Pittsburgh, Pittsburgh, PA; [4]Division of Surgical Oncology, Department of Surgery, University of Pittsburgh, Pittsburgh, PA

Surgical oncology continues to see the expansion of regional therapies for patients with advanced malignancy. This evolution and advance reaches far beyond cytoreductive surgery with hyperthermic chemoperfusion (CRS-HIPEC) to limb infusion and perfusions as well as isolated liver perfusion and hepatic artery directed therapies.

In this issue of *Annals of Surgical Oncology,* articles from the Seventh International Symposium on Regional Cancer Therapies have been solicited to offer insights into the management of advanced malignancies. These articles reveal the varied application of techniques in addition to addressing controversy, pointing to new technology, and forecasting the future in the field.

Within this series of manuscripts, 4 articles are dedicated to the management of appendiceal neoplasm. CRS-HIPEC is a well-established treatment for mucinous appendiceal cancers. Although the relationship between extent of resection and morbidity is well described, a paucity of data exists regarding the extent of resection and the oncologic outcome. Wagner et al. have reported experience with 282 patients with appendiceal carcinomatosis undergoing CRS-HIPEC. Within their series they examined a group undergoing "extensive" CRS and found this cohort did not have higher morbidity, mortality, or inferior oncologic outcomes compared with the control group of those with less extensive resection.[1]

The extent of resection is further addressed by Turaga et al. as they challenge the utility of a right colectomy for appendiceal mucinous adenocarcinoma. Questioning the added morbidity of the colectomy and the potential benefit of the removed nodal basin, they examined a cohort of more than 2000 patients from the SEER database. This report concludes that in the setting of metastatic disease or known node-positive disease there may be no benefit to right hemicolectomy.[2]

Understanding that high-grade appendiceal adenocarcinoma is rare and carries a worse prognosis than mucinous tumors, Turner et al. have shared their experience using a neoadjuvant chemotherapy approach for patients undergoing CRS-HIPEC. In a series of 45 patients with high-grade tumors, they demonstrated that those treated with a neoadjuvant approach had a 58 % response rate using imaging and biomarkers. The neoadjuvant approach did not appear to negatively impact the CRS-HIPEC procedure; however, the actuarial survival with this approach was not impacted.[3]

As long-term survival following CRS-HIPEC for appendiceal carcinoma is common, Low et al. have examined the value of MRI surveillance compared with serum markers in detecting early recurrence. Early detection is valuable as it allows for optimal repeated CRS-HIPEC and potentially more complete cytoreduction. In a series of 50 patients with recurrence, authors examined a cohort of patients with normal tumor markers but MRI evidence of recurrence and advocate for the value of surveillance MRI.[4]

Perioperative morbidity and mortality continue to be primary concerns for the administration of CRS-HIPEC. Canda et al. thoughtfully share their center's experience with this issue. Nonuniform reporting methods have historically produced variable results that are difficult to interpret. By using the NCI's criteria for adverse events (CTCAE) their center has demonstrated the impact in a manner that is reliable and potentially reproducible.[5]

In addition to appendiceal cancer, CRS-HIPEC regional therapies are also applied to ovarian, colon, rectal, gastric, and primary mesothelioma. Two articles highlight the application of CRS-HIPEC for mesothelioma and rectal

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T. Clark Gamblin, MD, MS
e-mail: tcgamblin@mcw.edu

cancer. In order to assess the efficacy of CRS-HIPEC for metastatic rectal cancer, Votanopoulos et al. compared rectal cases to colon cancer cases performed. They found no survival difference and point to the ability to perform a complete cytoreductive surgery as the determinant of survival. They conclude that rectal cancer carcinomatosis should not be uniformly excluded from CRS-HIPEC.[6]

Diffuse peritoneal mesothelioma is a rare malignancy that has been dramatically impacted by CRS-HIPEC. The role and timing of systemic chemotherapy with CRS-HIPEC for mesothelioma, however, is poorly defined. Deraco et al. have examined a large series of patients and compared those receiving preoperative systemic therapy with those treated postoperatively and to those receiving no systemic therapy. Although retrospective, they share intriguing data that preoperative systemic therapy did not add morbidity and that the variable regimens of systemic therapy did not appear to add to the benefit of CRS-HIPEC.[7]

With the introduction of newer chemotherapeutic agents for colon cancer, there has been a progression to consider them for regional therapies. Oxaliplatin is typically based on body surface area (BSA), and Leinwand et al. have examined if BSA predicts local or systemic exposure.They have demonstrated that BSA can be used to predict the pharmacokinetics of oxaliplatin-based HIPEC and that the volume of perfusate used with the drug correlates with the systemic exposure.[8]

Coupling the concept of new drugs with the effects of temperature, Pelz et al. have investigated the value of heated perfusate and its effects on gene expression. Although heat is widely accepted, authors sought to examine the optimal temperature with an in vitro model. They also used matching tumor samples before and after HIPEC to gauge the expression of specific heat shock proteins. This work points to potential new targets for therapeutic interventions in CRS-HIPEC.[9]

Although many quickly associate CRS-HIPEC as the primary modality of regional cancer therapy, many more patients with advanced malignancies receive regional liver-directed therapy. Focusing on a series of patients with inoperable neuroendocrine cancer, Arrese et al. have examined the impact liver-directed therapy had on patients with and without extrahepatic disease. They demonstrate a shorter overall survival for patients with extrahepatic disease; however, they show similar symptomatic, serologic and radiographic response in this group.[10]

The topic of limb infusion from 2 leading institutions provides important insights regarding associated morbidity and local response to treatment while attempting to predict response from plasma cytokine analysis. Isolated limb infusion is a minimally invasive procedure originally used to treat unresectable melanoma. In many centers, its application is currently used for unresectable soft tissue extremity sarcomas and other cutaneous malignancies. Wong et al. report their experience with limb infusion for current indications and demonstrate that repeated infusion treatment is not associated with increased toxicity and offers a similar disease response rate. Their large series with few complications and no amputations reinforces this important therapeutic option.[11] In an attempt to understand from preprocedure and pathologic factors who will respond to limb infusion for unresectable in transit melanoma, Shetty et al. have administered a cytokine assay on preinfusion plasma of patients who gained a complete response following therapy versus those who had progression of disease. This work emphasizes the marked decrease of immune-activating cytokines and further supports the role for immune-targeted therapy in patients with regionally advanced melanoma.[12]

In summary, it is our hope that this series of articles will provide valuable educational information regarding some of the options for patients with advanced malignancies. The series is a small representation of the evolving therapies available and provides further evidence of their potential, limits, and most importantly their impact. In addition, the series points to the future questions and challenges that teams face as we strive to improve our impact on cancer for the patient of tomorrow.

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