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EDITORIAL

The challenge of creating evidence-based clinical practice guidelines for the use of hyperthermic intraperitoneal chemotherapy in the management of peritoneal malignancies

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The management of primary and secondary malignancies of the peritoneum continues to pose a challenge to modern, multidisciplinary cancer care. The clinical practice guideline published by Auer *et al.* in this issue of *Current Oncology* provides a thorough and transparent review of the high-level evidence for hyperthermic intraperitoneal chemotherapy (HIPEC) with cytoreductive surgery (CRS)[1]. The guideline recommendations can be summarized as follows:

- For stage III primary epithelial ovarian or fallopian tube carcinoma, or primary peritoneal carcinoma, HIPEC should be considered after neoadjuvant chemotherapy at the time of interval CRS if optimal cytoreduction is achieved.
- For rare tumours, including malignant peritoneal mesothelioma and disseminated mucinous neoplasm of the appendix, the evidence is insufficient to recommend HIPEC with CRS as the standard of care, but patients should be referred to HIPEC specialty centres for assessment as part of an ongoing research protocol.
- The evidence is insufficient to recommend HIPEC with CRS for patients with colorectal, gastric, or recurrent ovarian carcinomatosis outside of a clinical trial.

This guideline is an excellent platform to discuss the contemporary management of peritoneal cancers in Canada and the current controversies.

The clinical practice guideline underwent internal and external review. Unfortunately, fewer than a quarter of the internal expert panel members came from centres with established peritoneal malignancy programs. The external review process was also lacking expert opinion from a high-volume peritoneal malignancy program in the United States or Canada (excluding Ontario). Although the aim of the review was to evaluate the additional benefit of HIPEC with CRS and not CRS alone, most of the primary treatment literature pairs those treatment modalities. In the absence of high-level evidence for the added value of HIPEC independent of CRS, the guideline recommendations default to the standard of care in Ontario, which is systemic chemotherapy or best supportive care. That approach is a departure from the current standard of care across the country for peritoneal disease of colorectal, appendiceal, and mesothelial origin. It also differs from the control arm (that is, CRS plus systemic chemotherapy) used in randomized controlled trials (RCTs) for the primary treatment of colorectal and epithelial ovarian carcinomatosis since the landmark Verwaal trial in 2003[2–4]. In Europe, clinical and patient equipoise have been lacking for more than 25 years with respect to the role of systemic therapy alone compared with CRS with or without intraperitoneal therapy plus systemic therapy for resectable carcinomatosis of colorectal and appendiceal origin[5].

It is important to note that the systematic review assessed only RCTs or comparative studies evaluating the addition of HIPEC to CRS. The narrow *a priori* inclusion criteria excluded data from a number of informative multicentre cohorts that inform expert opinion on the role of curative CRS plus HIPEC in the well-selected patient[5]. Observational studies can be designed in a manner to minimize bias and can provide high-quality data[6]. Indeed, the standard of care is frequently established without RCT evidence, as is the case for colorectal metastasectomy (for example, liver resection, lung resection). For rare or indolent peritoneal malignancies, observational evidence might be the only available data. In the case of low- and high-grade mucinous carcinoma peritonei of the appendix, the national and international consensus in light of the full breadth of the available literature is to offer, to appropriately selected patients, potentially curative CRS plus HIPEC rather than palliative systemic therapy[7,8].

A common misconception is that HIPEC is a single entity or protocol, when in fact, it simply refers to a method of chemotherapy administration. In the current systematic

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review, each RCT used a different HIPEC protocol. The choices of cytotoxic agent, dose, temperature, and dwell time can have a significant effect on cytotoxicity. It remains unclear whether one HIPEC protocol (for example, 35 mg/m^2 mitomycin C in 3000 mL for 90 minutes at 41–42°C) compared with another has an impact on clinically relevant outcomes. Indeed, a systematic review by Yurttas *et al.*[8] identified 86 different HIPEC protocols using just mitomycin C. The resulting uncertainty provides an opportunity for head-to-head comparisons in the treatment of more prevalent disease states (for example, colorectal carcinomatosis) and standardization of HIPEC protocols across peritoneal malignancy programs for indolent and rare histopathologies (for example, low-grade mucinous carcinoma peritonei of the appendix).

Even when peritoneal cancer is parsed apart by organ site, the evaluation of HIPEC as a regional therapeutic technique is complicated by competing and overlapping metastatic potential. We are just scratching the surface of the complex molecular profile and heterogeneous pattern of metastatic tropism of colorectal adenocarcinoma, one of the most common malignancies of the peritoneum. That complexity is not yet captured in the nascent body of RCT data, making any interpretation of the treatment effect of a particular HIPEC protocol difficult. It also highlights the importance of outcome selection in study design. Perhaps overall survival is an inappropriate benchmark for a regional technique, in which locoregional recurrence is a more relevant endpoint. Regional adjuncts to high-quality surgery in the management of other malignancies often fail to demonstrate an improvement in overall survival.

The guideline's recommendation that patients with rare peritoneal malignancies be referred to HIPEC speciality centres is salient. However, that recommendation should extend to all peritoneal cancers, and the referral centre should be one with a multidisciplinary peritoneal malignancy program. A centre of excellence in the surgical (CRS plus HIPEC) and medical management of peritoneal cancer is best positioned to participate and enrol patients into clinical trials and research protocols. Despite its recommendations, the current clinical practice guideline might hinder RCT enrolment if its recommendations are misinterpreted by referring physicians as a lack of clinical equipoise or of HIPEC efficacy as a treatment modality.

The clinical practice guideline for the use of HIPEC with CRS published in this issue of *Current Oncology* provides an excellent review of the current RCT evidence in this exciting field. The literature highlights the need for consensus, standardization, and prospective data collection by Canada's peritoneal programs. It also highlights the challenges of creating broad clinical practice guidelines for a biologically diverse group of diseases treated with a poorly defined intervention. Thoughtful consideration is needed in the implementation of the guideline recommendations, which are based on the absence rather than the presence of high-level data, and with respect to the impact that the guideline might have on the treatment options available to the well-informed patient.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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