

## Editorial

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# The concept of “Obstruction-Free Survival” as an outcome measure in advanced colorectal cancer management

<https://doi.org/10.1515/pp-2018-0101>

Despite improvements in diagnosis, imaging, surgical technique and chemotherapeutic agents, the majority of patients with synchronous, or metachronous, metastatic abdominal cancer ultimately die from the disease. In the context of advanced cancer, peritoneal malignancy is a particular problem, whether primary peritoneal malignancy (for example peritoneal mesothelioma) or peritoneal metastases from gastro-intestinal tract cancers. An added distressing, and life limiting, aspect of peritoneal malignancy is that bowel obstruction is common and often a terminal event. Malignant bowel obstruction is devastating for patients and distressing for relatives and healthcare workers, as it is often impossible to effectively palliate by medical treatments, endoscopic stenting or by surgical intervention. The combination of intestinal colic, with an inability to eat and drink, combined with the general need for a permanent nasogastric tube has major detrimental effects on the final period of a terminal illness.

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy have recently been established as a treatment strategy for selected patients with peritoneal malignancy of appendiceal [1] colorectal [2, 3], mesothelioma [4] and other malignancies within the peritoneal cavity. Despite successful intervention in some patients, the majority still succumb to disease and furthermore many are never suitable for CRS due to extent of peritoneal carcinomatosis.

The commonest tumours treated by CRS and HIPEC are peritoneal malignancy from the appendix [5, 6] or colorectal cancer [2]. Colorectal cancer can present with synchronous peritoneal disease or as metachronous

recurrence and in many cases recurrence may be peritoneal alone. In many patients peritoneal disease is extensive and best described as carcinomatosis and not amenable to complete removal by CRS. For this reason the concept of resectable colorectal peritoneal metastases [3] is a useful terminology in defining patients who are amenable to complete tumour removal and potential for cure in 20–30% of cases, though the remainder usually succumb from tumour recurrence. While optimal results are achieved with complete tumour removal (and ideally CCO surgery), it has also been noted that patients with CC1, or even CC2, may benefit if surgery is combined with HIPEC [7].

An anecdotal personal observation, over a number of years' experience with substantial numbers of patients, by the first author (BJM), has been the hypothesis that, despite high recurrence rates, after optimal CRS and HIPEC, bowel obstruction may be reduced where HIPEC has been administered. There are some potential mechanisms for this effect in that the most commonly used agent (Mitomycin C) has anti-adhesion properties and is used in ophthalmic surgery after tear-duct and other procedures to reduce scarring [8, 9]. There has also been some animal experimental work showing a reduction in intraperitoneal adhesions with Mitomycin C [10, 11].

In addition a cytotoxic effect on peritoneal tumour on the small bowel might have an additive effect. This hypothesis stimulates the concept of “obstruction free survival” as a new measure of a beneficial effect of intraperitoneal chemotherapy which may have profound effects on quality of life in patients with advanced cancer involving the peritoneum.

Indeed, in retrospect, the seminal paper by Sugarbaker et al. in 1985 [12], did suggest possible reduction in obstruction free survival. In this randomized trial 4/30 who had systemic chemotherapy required surgery for small bowel obstruction compared with 1/36 patients who had intra-peritoneal chemotherapy.

For many years we have been frustrated by the limitations of CRS and HIPEC due to poor outcomes in

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patients with high PCI scores, the high morbidity, occasional mortality and high cost with poor long-term outcomes when survival is the primary end point. For patients with diffuse carcinomatosis, up until now, there have been few alternative options. However, a recent major development in advanced peritoneal malignancy has been pressurized intra-peritoneal chemotherapy (PIPAC), which has benefits in disease control where complete tumour removal by CRS is not feasible [13, 14]. These advanced cases need new endpoints as long-term survival for most patients is unlikely.

Obstruction-free survival may be a true measurable benefit of PIPAC and HIPEC and should be included in all evaluations of these therapies in peritoneal malignancy. We may have over-looked real benefits to patients in the pursuit of the Holy Grail where cure is unlikely or impossible.

**Author contributions:** All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

**Research funding:** None declared.

**Employment or leadership:** None declared.

**Honorarium:** None declared.

**Competing interests:** The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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