

# CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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## The Role of HIPEC in Patients With Advanced Colorectal Cancer



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### H&O Which patients with colorectal cancer are eligible for treatment with HIPEC?

**Dr Bartlett** Intraperitoneal hyperthermic chemoperfusion (HIPEC) is appropriate for certain patients with colorectal cancer (CRC). The first hurdle is that the disease must be completely resectable. Other factors that play a role in the decision to use HIPEC include responsiveness to chemotherapy, extent of disease, and overall tumor biology. We prefer to use HIPEC for patients who have shown at least some response to systemic chemotherapy. If the patient has a negative prognostic factor, such as a poorly differentiated tumor, a *BRAF* mutation, or the presence of signet ring cells, we use HIPEC only if the patient has very minimal disease that has been completely resected and is responsive to chemotherapy.

### H&O Dr Ryan, are there any circumstances in which you recommend HIPEC for CRC?

**Dr Ryan** No, I don't use HIPEC for CRC, but I definitely recommend surgery if the surgeon can remove all the cancer. I do recommend surgery plus HIPEC for appendiceal cancer.

### H&O Dr Bartlett, do you also use HIPEC for appendiceal cancer?

**Dr Bartlett** Yes, although the data are no stronger for HIPEC in appendiceal cancer than they are for HIPEC in CRC. Appendiceal cancer is so rare that we have difficulty conducting randomized trials in patients with this disease, so we are more willing to use HIPEC in these patients in the absence of real data. Another situation in which we use HIPEC is peritoneal mesothelioma, which seems to have a unique response to HIPEC. Peritoneal mesothelioma is also a rare cancer, so we do not have the kind of data that we like to have to prove the efficacy of HIPEC, but it is used frequently in this setting, and we have seen remarkable results.

### H&O How much benefit would you say HIPEC adds to treatment in CRC?

**Dr Bartlett** We do not have the data we need to answer that question, but my impression is that HIPEC adds only a small amount. It is the combination of systemic chemotherapy, cytoreductive surgery, and intraperitoneal therapy that produces a good result. The most important components, in my opinion, are cytoreductive surgery and systemic chemotherapy. HIPEC has little downside, however, so I use it to enhance the effect of cytoreductive surgery.

### H&O Dr Ryan, do you think that HIPEC could add anything to the treatment of CRC?

**Dr Ryan** It definitely is possible, although it has not been proved. For example, it is possible that HIPEC has an immunogenic effect that we have undervalued. I would be open to clinical trials that looked at HIPEC and tried to prove that it works.

**H&O** What are the most important studies regarding the use of HIPEC in CRC?

**Dr Ryan** The Verwaal study initially showed a benefit of HIPEC when it was published in 2003, but this benefit did not persist with long-term follow-up at 8 years. Since

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then, the results of other studies of HIPEC also have been unfavorable. PRODIGE 7 (Systemic Chemotherapy With or Without Intraperitoneal Chemohyperthermia in Treating Patients Undergoing Surgery for Peritoneal Carcinomatosis From Colorectal Cancer), which was first presented at the annual meeting of the American Society of Clinical Oncology (ASCO) in 2018, was a flat-out negative study in terms of any benefit of the addition of HIPEC over cytoreductive surgery and standard chemotherapy alone. The COLOPEC study (Adjuvant HIPEC in High Risk Colon Cancer) also has been influential because it enrolled high-risk patients in the adjuvant setting. If there were ever an area in which HIPEC would make a difference, even a small one, we would expect to see it here. However, we could not discern a difference with HIPEC in that study either.

**H&O** Dr Bartlett, what is your take on these studies?

**Dr Bartlett** In the Verwaal study, the combination of HIPEC and cytoreductive surgery was beneficial. As Dr Ryan said, the survival rates began to overlap when the researchers looked at the 8-year survival. To me, this finding just means that there were not a lot of cures in that

patient population. There was a defined benefit to the therapy even though it did not cure the disease, which is typical of the results we expect with systemic chemotherapy for metastatic disease—eventually the curves are going to overlap.

The Verwaal study did not separate cytoreductive surgery from HIPEC, but I do not think that the addition of newer chemotherapies since then has negated the potential benefit of cytoreductive surgery and HIPEC. On the contrary, I think that newer chemotherapies would in theory add to the effect. When we did a propensity-matched study looking at newer chemotherapy agents alone or in combination with cytoreductive therapy and HIPEC, we showed a benefit from cytoreductive therapy plus HIPEC. (This study was published in *Cancer* in 2010 with Franko as the first author.)

The fact that the results of PRODIGE 7 and COLOPEC were negative may mean that cytoreductive surgery is effective on its own, and that HIPEC does not add anything. However, the HIPEC treatment used in those studies was different from that used in the Verwaal study. PRODIGE 7 and COLOPEC examined 30 minutes of HIPEC with oxaliplatin and mild hyperthermia, and both studies had negative results. To me, this means we should not be using the 30-minute oxaliplatin therapy for CRC anymore. The Verwaal study, on the other hand, examined 90 minutes of HIPEC with mitomycin-C and hyperthermia and produced positive results. I think the regimen used in the Verwaal study needs to be re-examined, and I think we can rally enough surgeons around accruing to that trial. The area where we have struggled in the past is getting someone to pay for the trial. We have tried a number of times to run trials through cooperative groups or through industry but have not been able to move forward from a financial perspective.

**H&O** Dr Ryan, what else would you like to say about the research?

**Dr Ryan** I would say that before COLOPEC and PRODIGE 7, the onus was on the HIPEC naysayers to participate in clinical trials and find out whether treatment did not work. Now that onus has shifted to the HIPEC proponents to prove that other ways of applying HIPEC are beneficial. The community of surgeons who use HIPEC at this point should be okay with another randomized study looking at HIPEC together with other regimens or other ways of applying it, and they should be comfortable randomly assigning their patients to a control arm of just cytoreductive surgery. Even after PRODIGE 7, some surgeons do not feel comfortable undertaking another randomized study because they believe that HIPEC is effective. However, the benefit

remains unproven, and I think we are going to see payers stop paying for this procedure in people with CRC unless we can prove a benefit.

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#### H&O What are the disadvantages of using HIPEC?

**Dr Ryan** Although in PRODIGE 7 mortality was uniformly low with surgery and HIPEC, morbidity was still fairly high. This is important because many of these patients actually have a chance at a cure. We are beginning to see some cases of long-term survival with multiple-agent chemotherapy, with approximately 20% or 25% of people living for 5-plus years on and off chemotherapy.

**Dr Bartlett** As a surgeon who has dealt with metastatic cancer for many years, one of my big concerns is that complications seem to increase the growth of cancer. A lot of data exist examining the mechanisms for this finding, especially when it comes to infectious complications. So, I agree with Dr Ryan that we need to worry about complications that can have a negative effect on cancer-related survival. It is extremely important that we perform high-quality surgery to avoid complications whenever possible.

We do not have a great deal of data regarding which procedure leads to complications—HIPEC or surgery. The only trial we have is PRODIGE 7, which has not yet been published. Presentations of PRODIGE 7 have shown an increased risk for complications in patients undergoing cytoreduction plus HIPEC vs those treated

with cytoreduction alone. The rate of intra-abdominal complications was not increased with HIPEC, however, so to me there is little downside to HIPEC. Patients who have had surgery and HIPEC recover very quickly unless their surgery was extensive. Although any increase in morbidity with HIPEC is very small, all of these procedures need to be performed at experienced centers so that complications do not negatively affect survival.

#### H&O What should the next step in research should be?

**Dr Bartlett** I think that randomized trials are key, so we need to figure out a way to move forward with them. HIPEC is just one of many possible therapies that may have an effect. Although we may see some cures with systemic chemotherapy and surgery, much room for improvement remains.

**Dr Ryan** I would agree with that—I think that’s spot on.

#### Disclosures

*Dr Bartlett has no disclosures. Dr Ryan has equity in MPM Capital and Acworth Pharmaceuticals, and has served in an advisory or consultant role for MPM Capital, Oncorus, Gritstone Oncology, and Maverick Therapeutics.*

#### Suggested Readings

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