Colorectal peritoneal metastases: Still a nihilistic outlook?

Authors: Narasimhan V^{1,3}, Pham T^{1,3}, Ramsay R^{1,3}, Heriot A^{1,2,3}, Warriar S^{1,2}

Affiliations:

¹ Peter MacCallum Cancer Centre, Department of Cancer Surgery

² Peter MacCallum Cancer Centre Department of Oncology

³ University of Melbourne

Corresponding author:

- Name: Dr Vignesh Narasimhan
- Email: Vignesh.narasimhan@petermac.org
- Phone: 0451121766

(Word count 1051 including references)

Conflicts of interest and disclosures:

The Authors have no conflicts of interest.

Dr Vignesh Narasimhan is a PhD Student and is a recipient of the Royal Australasian College of Surgeons Foundation for Surgery Research Grant, Colorectal Surgical Society Research Grant, NHMRC postgraduate scholarship and Peter MacCallum Foundation Scholarship outside the submitted manuscript.

Dr Toan Pham is a PhD Student and is a recipient of the Royal Australasian College of Surgeons Research Scholarship and Peter MacCallum Foundation Research Grant, outside the submitted manuscript.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/ans.14992](https://doi.org/10.1111/ans.14992)

The peritoneum is the third most common site of metastases from colorectal cancer¹, but carries the worst overall survival among all sites. Historically, patients with colorectal peritoneal metastases (CRPM) had a median overall survival of only 5.2 months². The reasons for this are believed to be multifactorial, including variable tumour biology, poor penetration of drugs into peritoneal tissue, resistance to standard chemotherapies, and an altered tumour microenvironment.

The advent and adoption of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS and HIPEC) offers a glimmer of hope to this otherwise nihilistic cohort. A structured online survey was recently circulated to all colorectal surgeons affiliated with the Colorectal Surgical Society of Australia and New Zealand. This survey provides some insight into the management approach to CRPM among local colorectal surgeons.

In the survey, most colorectal surgeons felt CRS and HIPEC should be managed at state-based specialised centres. The majority felt CRS and HIPEC significantly improves survival in appendiceal cancer, with some benefit in colorectal and ovarian cancers. While most agreed that a perforated cancer, ovarian or isolated peritoneal metastases at index operation carry the highest risk for peritoneal recurrence, many would still consider referral to gynae-oncology for a new ovarian mass after a colorectal cancer resection. Very few surgeons would favour a routine “second look” operation after high-risk resections. Overall responses from fellows, junior and senior surgeons were very similar.

In a randomised controlled trial (RCT), Verwaal et al demonstrated an improved overall and disease specific survival of 22.2 months with CRS and HIPEC compared to 12.6 months with systemic chemotherapy alone in the management

of CRPM³. Subsequent large volume studies have re-affirmed a significant survival benefit with CRS and HIPEC for CRPM, with a 24-45% 5-year survival, and the possibility of cure in a few⁴⁻⁶. The recent French PRODIGE 7 trial⁷ provided further evidence that high quality cytoreductive surgery performed at specialised peritonectomy centres can offer a median survival of 41.2 months with a 36.7% 5-year survival in patients with CRPM. When assessing the entire cohort, the addition of HIPEC did not improve overall survival, however on subgroup analysis, HIPEC did improve survival in patients with a peritoneal cancer index of 11 to 15. Nonetheless, the HIPEC protocol utilised in the trial is vastly different to those used elsewhere in the world and specifics around the application of HIPEC should remain an area of investigation. Whilst the Prodiges 7 results cannot be entirely extrapolated to the Australian setting given the significant difference in HIPEC protocols used in Australia, the impressive survival outcomes demonstrated in the trial provides strong evidence for the value of centralised high quality cytoreductive surgery. With the available data, the PRODIGE 7 trial should not change current practice in Australia and patients with isolated peritoneal metastases should be referred to a peritonectomy centre for consideration of CRS and HIPEC.

In ovarian cancer, Van Driel et al⁸ in a recent RCT demonstrated improved disease free and overall survival with CRS and HIPEC compared to CRS alone in advanced ovarian cancer. The authors believe that an ovarian mass after colorectal cancer should be considered a colorectal metastasis (krukenberg tumour) until proven otherwise, in line with its route of transcoelomic spread. Krukenberg tumours are considered peritoneal disease and should be referred to a peritonectomy centre for consideration of CRS and HIPEC.

Outcomes are more favorable from CRS and HIPEC when disease burden is lower. A pro-active approach to identify early CRPM with a “ second look

laparotomy” with CRS and HIPEC six months after high-risk resections led to detection of CRPM in 55% of patients, all of whom were asymptomatic⁹. Other novel approaches include the use of prophylactic or adjuvant HIPEC in high-risk cancers. However, more high-level evidence is required before these novel approaches can be brought into standard treatment. The results of randomised clinical trials such as ProphyloChip (NCT01226394) and COLOPEC (NCT02231086) will help better define the role of such pro-active approaches.

It is reassuring that colorectal surgeons, regardless of seniority have a similar approach to managing CRPM. CRS and HIPEC is the standard of care for CRPM in many countries. In Australia, the Cancer Council guidelines recommend referral to a peritonectomy centre for consideration of CRS and HIPEC for CRPM¹⁰.

CRS and HIPEC has proven benefit and offers a proportion of patients with a realistic glimmer of hope. Unfortunately, the majority of patients have high disease burden, and are not candidates for CRS and HIPEC. There is an urgent need to seek new therapies to help improve survival in the unresectable. In recent years, with advances in pre-clinical modeling of disease and immunotherapies¹¹, novel approaches such as personalised medicine or palliative options such as Pressurised Intra-Peritoneal Chemotherapy (PIPAC)¹² may be options to explore in the future.

References

1. Elferink MA, de Jong KP, Klaase JM, Siemerink EJ, de Wilt JH. Metachronous metastases from colorectal cancer: a population-based study in North-East Netherlands. *Int J Colorectal Dis.* 2015;30(2):205-12.
2. Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer.* 2000;88(2):358-63.
3. Verwaal V, van Ruth S, de Bree E, van Slooten GW, van Tinteren H, Boot H, et al. Randomized Trial of Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy Versus Systemic Chemotherapy and Palliative Surgery in Patients With Peritoneal Carcinomatosis of Colorectal Cancer. *Journal of Clinical Oncology.* 2003;21(20):3737-43.
4. Goere D, Malka D, Tzanis D, Gava V, Boige V, Eveno C, et al. Is there a possibility of a cure in patients with colorectal peritoneal carcinomatosis amenable to complete cytoreductive surgery and intraperitoneal chemotherapy? *Annals of Surgery.* 2013;257(6):1065-71.
5. Alzahrani N, Ferguson J, Valle S, Liauw W, Chua T, Morris D. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: long term results at St George Hospital, Australia. *ANZ J Surg.* 2016;86(11):937-41.
6. Elias D, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. *J Clin Oncol.* 2010;28(1):63-8.
7. Quenet F, Elias D et al. A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7. *J Clin Oncol* 36, 2018 (suppl; abstr LBA3503)
8. van Driel WJ, Koole SN, Sikorska K, Schagen van Leeuwen JH, Schreuder HWR, Hermans RHM, et al. Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer. *N Engl J Med.* 2018;378(3):230-40.

9. Elias D, Goere D, Di Pietrantonio D, Boige V, Malka D, Kohnen-Shahri N, et al. Results of systematic second-look surgery in patients at high risk of developing colorectal peritoneal carcinomatosis. *Ann Surg*. 2008;247(3):445-50.
10. Cancer Council Australia Colorectal Cancer Guidelines Working Party. Clinical practice guidelines for the prevention, early detection and management of colorectal cancer. Sydney: Cancer Council Australia. [Version URL: <https://wiki.cancer.org.au/australiawiki/index.php?oldid=180618>, cited 2018 Jul 18].
11. Vlachogiannis G, Hedayat S, Vatsiou A, Jamin Y, Fernandez-Mateos J, Khan K, et al. Patient-derived organoids model treatment response of metastatic gastrointestinal cancers. *Science*. 2018;359(6378):920-6.
12. Demtroder C, Solass W, Zieren J, Strumberg D, Giger-Pabst U, Reymond M. Pressurized intraperitoneal aerosol chemotherapy with Oxaliplatin in colorectal peritoneal metastasis. *Colorectal Dis*. 2016 Apr;18(4):364-71

Colorectal peritoneal metastases: Still a nihilistic outlook?

Authors: Narasimhan V^{1,3}, Pham T^{1,3}, Ramsay R^{1,3}, Heriot A^{1,2,3}, Warriar S^{1,2}

Affiliations:

¹ Peter MacCallum Cancer Centre, Department of Cancer Surgery

² Peter MacCallum Cancer Centre Department of Oncology

³ University of Melbourne

Corresponding author:

- Name: Dr Vignesh Narasimhan
- Email: Vignesh.narasimhan@petermac.org
- Phone: 0451121766

(Word count 1051 including references)

Conflicts of interest and disclosures:

The Authors have no conflicts of interest.

Dr Vignesh Narasimhan is a PhD Student and is a recipient of the Royal Australasian College of Surgeons Foundation for Surgery Research Grant, Colorectal Surgical Society Research Grant, NHMRC postgraduate scholarship and Peter MacCallum Foundation Scholarship outside the submitted manuscript.

Dr Toan Pham is a PhD Student and is a recipient of the Royal Australasian College of Surgeons Research Scholarship and Peter MacCallum Foundation Research Grant, outside the submitted manuscript.

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Narasimhan, V;Pham, T;Ramsay, R;Heriot, A;Warrier, S

Title:

Colorectal peritoneal metastases: still a nihilistic outlook?

Date:

2019-09-01

Citation:

Narasimhan, V., Pham, T., Ramsay, R., Heriot, A. & Warrier, S. (2019). Colorectal peritoneal metastases: still a nihilistic outlook?. ANZ JOURNAL OF SURGERY, 89 (9), pp.996-997.
<https://doi.org/10.1111/ans.14992>.

Persistent Link:

<http://hdl.handle.net/11343/286359>