Contemporary management of advanced colorectal cancer: the Australian experience

Colorectal cancer (CRC) is the third most common cancer in Australia, with almost 16 000 new cases in 2022 accounting for 10% of new cancer diagnoses and 11% of cancer-related deaths.[1] There has been a well documented increase in the incidence of CRC in people under the age of 50 years in Australia in recent decades, while the incidence in those older than 50 years has decreased over the same period.[2] Treatment of CRC has evolved dramatically in the 21st century, particularly for patients with advanced disease. Advances in medical imaging and peri-operative medicine, as well as refinement of surgical techniques, have facilitated radical resection in selected patients with advanced or recurrent local disease, as well as those with limited metastases, who would otherwise be considered incurable. Improvements in systemic therapy mean that, in contemporary practice, many patients with metastatic (stage IV) CRC who historically had few systemic treatment options and a poor anticipated survival may now be afforded durable disease control and have a life expectancy measured in years rather than months. CRC is increasingly understood to be a biologically heterogenous disease. As the behaviour of individual tumours is better characterised by their molecular profiles, targeted systematic therapy combined with ablative techniques and radical surgery in selected patients can be expected to further improve outcomes. This article describes recent developments in the management of advanced CRC and how these advances are reflected in contemporary Australian practice.

Locally advanced and recurrent rectal cancer

In the past five years there have been major developments in the type and sequence of neoadjuvant therapy (radiotherapy, chemotherapy, immunotherapy) used for treatment of patients with primary rectal cancer. For those at high risk of disease recurrence, prioritising systematic chemotherapy, with or without radiotherapy, before surgery (in a total neoadjuvant approach) is now well established in Australia. This may increase the proportion of patients who achieve a complete response to neoadjuvant treatment and where the possibility of avoiding surgical resection altogether and instead pursuing intensive surveillance in a watch and wait approach is a possibility. Watch and wait remains controversial and is currently being investigated by the Australian RENO trial (ACTRN12619000207112; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=376810) as well as internationally,[3] and may be offered in selected patients at many local centres.

For patients who present with locally advanced tumours that invade adjacent organs, or those who develop local recurrence after treatment of a primary cancer, radical resection of the tumour with all involved adjacent structures is the only potentially curative treatment. Multi-visceral resection for locally advanced or recurrent rectal cancer (pelvic exenteration surgery) presents a particular challenge due to the confines of the bony pelvis which limits surgical access to the tumour, and the proximity of major neurovascular structures makes attempts at resection potentially hazardous. Owing to these concerns, as well as initially high rates of post-operative morbidity, pelvic exenteration has historically not been well accepted by the surgical community, particularly in patients with locally recurrent rectal cancer. However, significant technical advancements in the past two decades, led in many cases by specialist exenteration units in Australia and New Zealand,[4] have dramatically improved the oncological outcomes of this radical procedure. Pelvic exenteration for rectal cancer is now performed routinely and safely at specialist referral centres, with contemporary 5-year survival rates of 65–75% for primary tumours and 45–53% for recurrent tumours.[5,6] In 2024, pelvic exenteration is considered the standard of care for selected patients with locally advanced and recurrent rectal cancer. In patients who choose not to pursue or are not eligible for surgery, stereotactic body radiotherapy combined with systematic chemotherapy, although not curative, may achieve durable disease control for some.[7]

Solid organ metastases

About 20–25% of patients with CRC have metastatic (stage IV) disease at the time of diagnosis, of which a proportion may be curable. Resection of CRC liver and lung metastases, both previously uniformly fatal conditions, are now well established, with long term survival achievable in up to 50% of patients with single organ metastases.[8,9] Although hepatic resection was traditionally only considered in patients where the pattern of disease met specific anatomical criteria (number, size and location of metastases), this has evolved dramatically, and in contemporary practice the indication for liver resection is the ability to completely and safely resect all disease while preserving an adequate liver remnant. For patients with resectable hepatic metastases, the role of chemotherapy and how it should be integrated with surgery is the subject of ongoing debate. For patients with initially unresectable hepatic metastases, upfront systemic chemotherapy (with or without combined targeted agents) may downstage lesions and, in combination with adjunct techniques such as portal vein embolisation, convert unresectable to resectable (and potentially curable) disease.

In patients with metastases in more than one organ (eg, the liver and lung), the boundaries of what constitutes potentially resectable disease continues to expand. Local non-resectional ablative techniques, including thermal ablation and stereotactic body radiotherapy, may be used in combination with metastastectomy to remove or ablate all macroscopic disease. This

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oligometastatic disease may be encountered at various time points over the continuum of treatment (eg, at first diagnosis or after different lines of treatment), and it is critical that patient selection for metastastectomy in this setting is made in a multidisciplinary context and is based on an understanding of the biological behaviour of the individual tumour. In an area where there are limited data to guide decision making, the sequence of treatments (ie, resection of the primary tumour, treatment of metastases, and systematic therapy) must be determined on an individual basis with consideration given to the timing of onset (synchronous or metachronous), location and size of metastases, response to previous lines of treatment, molecular tumour characteristics such as *RAS, BRAF* and mismatch repair gene mutational status, as well as patient factors including fitness and preference.

Peritoneal metastases

The peritoneum is the second most common site of metastases after the liver, and peritoneal metastases occur in about 10% of patients with CRC. These may be diagnosed at the same time as the primary tumour (synchronous metastases) or during subsequent surveillance (metachronous metastases). Peritoneal metastases have historically carried a poor prognosis, with older systemic chemotherapy treatment regimens based on 5-fluorouracil associated with a median survival of 6 months.[10] Although this has improved with newer agents such as oxaliplatin, leucovorin and irinotecan, as well as targeted agents such as epidermal growth factor receptor inhibitors (eg, cetuximab), treatment with systemic therapy alone remains palliative likely due to poor drug penetration of the peritoneum and lack of local ablative options.

Cytoreductive surgery (CRS), which involves the combination of visceral resections and peritonectomy procedures to remove all macroscopic tumour deposits, combined with hyperthermic intraperitoneal chemotherapy (HIPEC), is a radical treatment strategy for patients with peritoneal surface malignancy of various origins that was developed in the 1990s. Results from a randomised trial became available in 2003 and showed that CRS combined with HIPEC was associated with longer overall survival than systemic chemotherapy alone.[11] Based on these data as well as other studies, this radical treatment became established as a potentially curative treatment option in highly selected patients with low volume disease, with contemporary series reporting 5-year overall survival rates of 23–52%.[12] Patient selection, based on excellent performance status, a low burden of disease and an understanding of the biological behaviour of the individual tumour, is key to achieving these encouraging outcomes.

In 2017, the ANZ Peritoneal Malignancy Collaboration was established and plays an important role in coordinating collaboration between the eight peritoneal malignancy centres in our region. Recent results of the PRODIGE 7 trial, which reported no survival benefit from the addition of HIPEC to CRS alone,[13] raised controversy around the use of HIPEC. Due to multiple limitations of the PRODIGE 7 trial design which question the validity of its results, most members of the ANZ Peritoneal Malignancy Collaboration continue to use HIPEC,[14] and pilot work for a collaborative multicentre trial that aims to tailor the choice of HIPEC agent to an individual patient's tumour is underway.

The ability to remove all macroscopic disease is one of the most important predictors of survival following CRS and HIPEC. Unfortunately, in a significant proportion of patients with CRC, peritoneal metastases are diagnosed late when the intraperitoneal volume of disease is high and/or incurable distant metastases are also present, rendering the patient ineligible for this treatment. For this group of patients, pressurised intraperitoneal aerosolised chemotherapy is a minimally invasive approach currently under investigation at some Australian centres and may be a feasible method for disease control.[15]

Systemic treatments

Importantly, while cure is the understandable hope, it must be remembered that most patients with stage IV CRC will develop disease recurrence, and that the aim of treatment is to prolong disease control and maintain quality of life. For patients with unresectable metastatic CRC, advances in systemic treatments have led to incremental improvements in survival. The addition of irinotecan (a topoisomerase I inhibitor) and oxaliplatin (a DNA cross-linking agent) to 5-fluorouracil in the early 2000s, followed by the development of targeted anti-vascular endothelial growth factor (bevacizumab) and anti-epidermal growth factor receptor (cetuximab) monoclonal antibodies have improved the anticipated survival of most patients with metastatic CRC to 24–36 months. More recently immunotherapy agents, such as nivolumab and pembrolizumab (anti-PD-1) and ipilumumab (anti-CTLA-4), have been incorporated into the treatment of patients with mismatch repair deficient CRC in both the metastatic and neoadjuvant settings.[16,17] Use of targeted agents continues to be refined and further improve outcomes, such as the recent use of combined triplet targeted therapies (encorafenib, cetuximab, and binimetinib) for patients with *BRAF* V600E-mutated CRC, which resulted in longer survival than standard therapy in the BEACON trial.[18] These represent important steps toward tailored therapy which, combined with selective metastastectomy and ablative treatments, is expected to continue to improve outcomes for this group of patients in the emerging era of precision medicine.

Future directions

The developments in management described above have driven the natural evolution of a small number of advanced CRC units in Australia and New Zealand, which are able to deliver complex surgery (such as pelvic exenteration, cytoreductive surgery, and metastectomy), local ablative treatments by percutaneous approaches or stereotactic radiotherapy, as well as access to novel systemic treatments and

clinical trials. The clinical need for such centres is likely to grow with increasingly complex and personalised multimodal treatment regimes, which require specialised multidisciplinary planning. Coordinated development and adequate funding of these centres is critical to allow them to support these referrals, and establishing accessible referral pathways will help to ensure that all patients with advanced CRC in Australia and New Zealand have timely access to all treatment options.

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