COLORECTAL CANCER

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Abstract

Major advances in the prevention, diagnosis and both curative and palliative management of colorectal cancer have occurred in the past 40 years. Australian clinicians have been at the forefront through involvement in basic, translational and clinical trials research, through the Clinical Oncological Society of Australia and the various cooperative trials groups, including the Australasian Gastrointestinal Trials Group and the Trans Tasman Radiation Oncology Group. The Australasian Gastrointestinal Trials Group has successfully facilitated more than 50 clinical trials across all disciplines and allows national investigators to bring to fruition clinical and translational research questions in an academic environment. The Clinical Oncological Society of Australia's role in facilitating research, education and multidisciplinary interaction in colorectal cancer has impacted on improving patient care.

Prevention

Strong evidence regarding the role of diet, weight control and exercise, in both primary and secondary prevention, has led to increasing community awareness regarding the nexus between healthy lifestyle and cancer. Agents such as aspirin and COX-2 inhibitors are being investigated for their cancer prevention activity, via action on anti-inflammatory pathways, following demonstration of reduced colorectal cancer (CRC) incidence in the large studies of their use for cardiovascular and stroke prevention.[1]

Screening

Although covered in a companion article, it would be remiss not to mention the solid evidence for faecal occult blood testing (FOBT) which has led in Australia to the government funded National Bowel Cancer Screening Program, which is still to be fully rolled out.[2] Issues of funding for repeat testing at five yearly intervals, and of adequate and timely colonoscopy services to follow-up positive tests, remain on the agenda.

Diagnosis

Technological advances in imaging have seen significant improvements in CRC staging. With CT then MRI, staging of primary and detection of secondaries are now much more accurate. MRI staging is funded and standard of care for rectal cancers, although expertise in interpretation is required. PET scanning in combination with CT has also improved selection of patients with limited liver metastases who are suitable for curative hepatic resection.

Surgery

Many advances have occurred, with the routine implementation now of total mesorectal excision (TME) for rectal cancer and laparoscopic, rather than open procedures, where appropriate. Australian surgeons led a randomised trial demonstrating equivalence of laparoscopic with open resection for colon cancers (ALCCaS study),[3] and are currently randomising patients in the AGITG Australasian Laparoscopic Cancer of the rectum Trial (A La CaRT).[4] The rigorous assessment in clinical trials of surgical techniques is a tribute to the academic nature of Australian surgeons, and is reflected by the training and accreditation of members belonging to the Colorectal Surgical Society of Australia and New Zealand. Given the repeated demonstration of superior outcomes for patients with CRC managed by specialist surgeons,[5] there is an awareness of the importance to patients of receiving care from specialised teams. Other major advances have included surgical stapling techniques to allow ultralow anastomoses, leaving very few patients with a permanent stoma.

Surgery now plays an important role for patients who relapse with liver limited metastases that are accessible to resection, either before or following systemic chemotherapy. The ability to cure up to 50% of patients in this circumstance (or with isolated lung metastases) is truly a paradigm shift.

Multidisciplinary teams

Perhaps the most important advance over the past 20 years has been the recognition of the multidisciplinary teams, usually including surgeons, medical and radiation oncologists, stomal therapists, nursing and allied health members and radiologists and pathologists among others. Multidisciplinary team meetings, where individual cases are reviewed and optimal management discussed, have facilitated equity for patients in accessing best practice. As a multidisciplinary organisation, COSA has provided the model on which these multidisciplinary teams are based and has laid the foundation for combined education, research, debate, discussion and open disclosure.

Chemotherapy

Advances have been made in adjuvant chemotherapy, with combination chemotherapy now standard for Stage III disease. Ease of administration of chemotherapy has been improved using central venous access devices (CVAD) that can be inserted under local anaesthetic (by interventional radiologists) and facilities for disconnection of infusers by community nursing teams. Trials demonstrating at least equivalence, if not superiority, of the fluoropyrimdine capecitabine, have opened options for patients, as this is an

oral agent, thereby removing the need for a CVAD if given as a single agent. It is particularly useful for patients from rural and remote settings.

Disappointingly, recent trials (with large Australian participation) of adding the new targeted therapies which are beneficial in the treatment of advanced CRC, to adjuvant therapy have been negative. The AGITG has been a world leader in trials in CRC, both local investigator initiated academic trials and those developed in collaboration with other national trials groups. Current studies include the SCOT, study examining whether a shorter duration (three months) of adjuvant chemotherapy is non-inferior to the standard six months.[6]

Many chemotherapy options now exist for patients with metastatic CRC, with median survival of patients now more than two years, and 10-15% patients living more than four years, compared to less than six months 40 years ago. The addition of 'targeted therapy' to standard chemotherapy agents has incrementally improved survival: the antiangiogenic antibody bevacizumab and the EGFR-inhibiting antibodies, being two classes which have now entered routine practice, with others on the verge. However, the most exciting development is the paradigm shift towards 'personalised medicine', aiming to match specific treatments with the tumour and patient genotype. The landmark identification of the KRAS gene as being predictive of response to anti-EGFR agents was led by Christos Karapetis.[7] Further translational studies are being undertaken to refine the subgroups that respond to medication to achieve the core of 'individualised therapy'. It is gratifying to be involved with many COSA investigators in trials such as the current AGITG ICECREAM study, examining the role of cetuximab (EGFR-inhibitor) in patients whose tumour bears a KRAS G13 D mutation.[8] AGITG studies have also included the MAX study and the CO20 studies, both establishing standard of care in CRC treatment, involving not only tumour assessment but quality of life and patient preferences.

Radiation therapy

MRI staging of rectal cancers has allowed identification of patients with locally advanced tumours (T4 and/or N1 and/or high risk T3) where trials have clearly shown improved outcome with preoperative chemoradiation. The landmark TROG study established equivalence of short course (five days) of preoperative RT compared to long course (six weeks chemoradiation) for most patients.[9] New techniques such as IMRT and incorporating PET/CT imaging into planning have reduced treatment toxicity and are likely to improve outcomes.

Psychosocial care, survivorship and supportive and palliative care

These areas have been addressed in other articles in this edition, but are mentioned here to emphasise their importance as vital parts of the advances in management of patients with CRC.

Translational research

CRC has been at the forefront of the paradigm shift to personalised medicine. Collaboration between basic scientists and clinicians has facilitated better understanding of the pathogenesis and clinical behaviour of CRC at a genetic and cellular level. New therapies are targeting vulnerable pathways within the CRC cell, and biomarkers which predict for prognosis and most importantly, response to therapy, are increasingly aiding selection of patients for the most effective treatments. By correlating banked tissue and blood samples, clinical trials in CRC are the best vehicle for studying the complex behaviour of the cancer cell.

Rural and regional centres and the Asia-Pacific region

The emphasis on provision of care in rural and regional centres has allowed COSA input into government policies and decisions contributing to improved resources, including provision of radiation services, PET scanning etc, so that most patients with CRC can be treated within a reasonable distance of their homes, but still within a centre of sufficient volume and expertise. Supporting rural and regional clinicians to become involved in clinical trials has led to increased recruitment of patients from this demographic.

The improving economic conditions in the very populous countries in our region provide opportunities and challenges for leadership from COSA. Active engagement with China, Singapore and many other countries through COSA's Developing Nations Program and the interest and engagement of leading clinicians, allows us to play a significant role in enhancing the lives of patients with CRC beyond Australia.

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