

response. In a phase 3 study,⁹ nearly 60% of patients with advanced renal cell carcinoma achieved a response with combinations such as axitinib (a VEGF inhibitor) with pembrolizumab. Similarly, for patients with non-small-cell lung cancer and high tumour mutational burden (\geq ten mutations per megabase), in the phase 3 CheckMate 227 trial¹⁰ 45% achieved a response rate with nivolumab plus ipilimumab compared with 27% achieving a response with chemotherapy.

Considering the caveats of cross-trial comparisons, pegylated IL-10 with checkpoint inhibition seems to produce similar results at best, suggesting that it would not displace these combinations in a randomised study designed to assess its superiority as initial therapy in patients with renal cell carcinoma and without any patient selection. One advantage offered by the combination of pegilodecakin with pembrolizumab or nivolumab² was the favourable adverse event profile with an easily managed spectrum of toxicities (most notably anaemia, thrombocytopenia, and fatigue). The presented data did not address the possibility of pegylated IL-10 in the salvage setting for renal cell carcinoma and non-small-cell lung cancer; however, the data for melanoma (in a largely checkpoint-inhibitor pre-treated cohort) did not provide much support for this approach. The key next step for further development of this combination, and all combination strategies designed to improve the efficacy of checkpoint inhibitors, is to fully understand the mechanisms of response of each combination and develop biomarkers to select patients who would most likely respond.

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Complete mesocolic excision for colon cancer: is now the time for a change in practice?

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Complete mesocolic excision for colon cancer has gained increasing popularity over recent years following publication of the Erlangen experience in 2009.¹ The investigators of this study¹ standardised their surgical approach for potentially curative disease, leading to a reduction in local recurrence (from 6.5% to 3.6%) and improvement in cancer-related 5-year survival (from 82.1% to 89.1%) over a 24-year period. Complete mesocolic excision is based on similar principles to

total mesorectal excision for rectal cancer, a technique now considered the international gold standard. Total mesorectal excision has led to substantial improvements in outcomes through removal of the tumour in an intact package containing all major routes of dissemination.²

Optimal complete mesocolic excision surgery comprises three important components: the specimen should be removed in the mesocolic plane ensuring

that the mesocolic fascia and peritoneum remain intact; the supplying vessels should be ligated at their origin; and a sufficient length of the colon should be removed. Good evidence exists to support the fact that integrity of the mesocolic plane is important, with a 15% improvement in 5-year overall survival reported between the best and worst specimens for all cases, increasing to 27% in stage III disease.³ A theoretical advantage exists for a high (D3) versus an intermediate (D2) or low (D1) vascular ligation, in which additional central lymph nodes will be removed, thus reducing the chances of residual metastatic disease. However, the size of the effect and the patient population who benefit from high vascular ligation are not well defined. Despite the principles of mesocolic plane surgery being relatively well accepted, although not necessarily widely practised, the concept of high vascular ligation remains fiercely debated because of the scarcity of robust evidence and association with increased morbidity in some studies.⁴ By contrast, there is no good evidence that extended length of colon resection 10 cm beyond the tumour offers any oncological advantage.⁵

Surgeons from Hillerød, Denmark, were convinced by the argument for complete mesocolic excision at an early stage and implemented this technique as the standard procedure in Nordsjællands Hospital, Hillerød, from June, 2008. Independent pathological review soon after standardisation showed that Hillerød specimens were oncologically superior when compared with the other regional hospitals practicing non-complete mesocolic excision surgery, with a greater mesocolic plane prevalence (75% vs 48%) and distance between the tumour and vascular tie (median 105 mm vs 84 mm in fresh specimens from all tumour sites).⁶ Early outcomes suggested that complete mesocolic excision in Hillerød was associated with improved disease-free survival.⁷ In *The Lancet Oncology*, Claus Bertelsen and colleagues' study⁸ reports the 5-year outcomes for right-sided colon cancer across the Capital Region of Denmark, demonstrating a significant reduction in recurrence to 9.7% (95% CI 6.3–13.1) in patients of the complete mesocolic excision group versus 17.9% (15.3–20.5) for those undergoing non-complete mesocolic excision surgery (ie, the control group) in patients with potentially curative stage I–III disease. A notable difference was observed in lymph node yield between

the complete mesocolic excision group and the control group (median 38 vs 21), which is often used as a surrogate endpoint of surgical quality. This finding is unlikely to be explained by central ligation, since independent specimen morphometry has previously shown only 11 mm of additional tissue between the bowel wall and high tie with complete mesocolic excision surgery.⁶ Instead, this finding is more likely to reflect the use of ancillary lymph node identification techniques and the increased length of colon resected, with longitudinal nodes not thought to be of great oncological importance.⁵ It is not stated whether apical node involvement was reduced with complete mesocolic excision.

There are some key limitations to Bertelsen and colleagues' study.⁸ The data presented focus purely on right-sided colon cancers, with no long-term follow-up presented for distal transverse and left-sided tumours, unlike the early outcomes study.⁷ Whether this omission reflects a failure to replicate the long-term benefit of complete mesocolic excision in these tumours remains unclear. Moreover, it is disappointing that the key determinants of complete mesocolic excision quality—ie, mesocolic plane and vascular ligation height—have been excluded from the analysis. Although assessment of the mesocolic planes is somewhat subjective, it is possible that much—if not all—of the benefit of complete mesocolic excision surgery is derived from simply removing the specimen intact, with relatively little (if any) additional benefit from high ligation. The benefit of high ligation could be undone by mesocolic disruptions, leading to tumour dissemination; therefore, in the absence of a robust study with standardised mesocolic plane surgery (backed up by rigorous pathological quality control) comparing high versus intermediate level ligation, the opponents of complete mesocolic excision will still argue their case.

Despite these limitations, Bertelsen and colleagues should be widely congratulated. It is enlightening to see a group of committed surgeons with multidisciplinary support transforming their long-term oncological outcomes for right-sided colon cancer through meticulous complete mesocolic excision surgery. Although the high versus intermediate ligation question might remain, all medical teams treating colon cancer should be encouraged to refocus on their practice to ensure that long-term outcomes improve in line with those



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reported for rectal cancer. Perhaps now might be the time for a change in practice.

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Maintenance chemotherapy in rhabdomyosarcoma: the new standard of care



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In *The Lancet Oncology*, Gianni Bisogno and colleagues¹ present the results of an important frontline, phase 3 randomised study in children and adolescents with rhabdomyosarcoma. This trial was done by the European paediatric Soft tissue sarcoma Study Group (EpSSG) cooperative group, in children and adolescents with previously untreated high-risk non-metastatic rhabdomyosarcoma, and shows the benefit of six cycles of vinorelbine and oral cyclophosphamide maintenance chemotherapy in this subgroup of patients.

Although rhabdomyosarcoma is the most common soft tissue sarcoma in children, the disease is still rare, with about 400 newly diagnosed cases each year in Europe and a similar incidence in the USA. Rhabdomyosarcoma consists of two distinct molecularly defined cancers. Tumours with *PAX-FOXO1* fusions (either *PAX3* or *PAX7*) show alveolar histological features and usually do not have other somatic mutations. Fusion-negative tumours most often have embryonal histological characteristics and harbour mutations in key signalling pathways.² Unfortunately, at present we do not have the tools to target these alterations, nor have we found substantial differences between fusion-positive and fusion-negative tumours in their response to cytotoxic chemotherapy. As is typical for frontline rhabdomyosarcoma trials, this EpSSG study included both biological entities, which increased the heterogeneity of the study population.

Although cooperative group studies in Europe, Australia, New Zealand, and North America initially³ made great strides in improving outcomes with the introduction of multi-agent chemotherapy, these results have plateaued in recent decades.³ These previous studies tested many classes and combinations of chemotherapy drugs with clinical activity in rhabdomyosarcoma, including alkylating agents (cyclophosphamide, ifosfamide, melphalan, and trofosfamide), anticancer antibiotics (dactinomycin, doxorubicin, and idarubicin), vinca alkaloids (vincristine and vinorelbine), epipodophyllotoxins (etoposide), and camptothecins (topotecan and irinotecan). Before this EpSSG trial, all studies that added other active chemotherapy drugs to standard treatment (an alkylator [ifosfamide or cyclophosphamide], vincristine, and dactinomycin) did not report improved outcomes. As suggested in a commentary discussing the previous European rhabdomyosarcoma study, perhaps the issue is not that we do not have enough cards (ie, cytotoxic drugs) in our deck, but that we have not learned to play them well.⁴

This EpSSG study had some flaws. The background supporting this maintenance combination was sparse, based on two studies led by Casanova and colleagues: a single-agent vinorelbine trial (with six of 12 patients with rhabdomyosarcoma achieving objective responses)⁵ and