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Manuscript

When cancer immunotherapy is featured on the front pages of Time Magazine (1), the Australian Financial Review (2) and The Economist (3), there is a common realisation of the importance and significant impact that immunotherapy is having on advancing cancer therapy. Not since the discovery of chemotherapy in the late 1940s has there been such a rapid and substantive impact on cancer outcomes.

So what does the future hold for cancer surgery with the dawn of the immunotherapy?

Immunotherapy describes the utilisation/reactivation of the host immune system to eradicate cancer cells. A struggle between cancer cells and the immune system rages within a cancer patient, which can be summarised by three E's: *Elimination*, *Equilibrium* and *Escape* (4). The majority of malignant cells will be *eliminated* before they take root, however some generate a sanctuary whereby equilibrium between tumour growth and immune destruction is reached. Those that eventually *escape* immune control progress to locally advanced and metastatic disease.

The founding father of immunotherapy was William Coley, an orthopaedic surgeon, who in 1891 injected a mixture of dead bacteria into a patient to elicit an immune-mediated regression of sarcoma. However, limited capacity at the time to adequately understand the biology of the tumour microenvironment, coupled with the advent of more effective

treatment modalities such as radiation and cytotoxic chemotherapies, immunotherapy took a back seat until the 1970s. The renaissance of immunotherapy began with the discovery of the T-cell growth factor, Interleukin-2 (IL-2), in 1976. IL-2 was used to boost anti-tumour lymphocyte activity against melanoma and renal cell carcinoma (5), albeit with significant toxicity and thereby limited success. The problem wasn't that the T-cells needed further stimulation but rather was they were being inhibited from attacking cancer cells by immune checkpoint molecules; these include PD-1/PDL-1 and CTLA-4. Checkpoint inhibitor blockade disrupts these 'brakes' thus enhancing T-cell recognition and killing of cancer cells.

The impressive successes of checkpoint inhibitors: ipilimumab (Yervoy®), pembrolizumab (Keytruda®) and nivolumab (Opdivo®) in melanoma has expanded to multiple other tumour types including non-small cell lung cancer, microsatellite unstable colorectal cancer, gastric cancer, urothelial carcinoma, and metastatic head and neck squamous cell carcinoma. The first immune checkpoint inhibitor agent used clinically was ipilimumab, an anti-CTLA-4 antibody that enhances the activation of T-cells in lymphoid tissue for the treatment of unresectable or metastatic melanoma (6). Following this, pembrolizumab and nivolumab were employed, blocking the suppressive interaction between the PD-1 receptor (on T-cells) and its ligands PD-L1 (on cancer cells). The underlying premise of checkpoint inhibitor blockade is that they are most effective in immunogenic cancers (predominantly those with a high mutation burden), and hence currently are effective in less than 20% of cancers. Recent serendipitous observations of ongoing tumour control even after discontinuation of

immune checkpoint therapy has brought much excitement as the implication is enormous for patients with metastatic disease who have been through multiple lines of chemotherapy (7).

An emerging alternative is adoptive cellular therapy, where primary or metastatic tumours are surgically resected and tumour-specific lymphocytes are then extracted and expanded ex-vivo. These are then re-introduced to the patient after systemic lympho-depletion therapy. Currently, there are adoptive cellular therapy trials targeting melanoma, head and neck, renal and gynaecological malignancies. This has led to an additional indication for metatasectomy, which was once considered futile, but is now being used as a source to enrich tumour-specific lymphocytes for this novel therapy (8).

All this said it remains that the majority of cancers are not easily detected by the immune system and thus different strategies such as cancer vaccination against neo-antigens or differentially over-expressed self-antigens have become topical; successful examples include Sipuleucel-T (Provenge®) against castrate-resistant prostate cancer (9) and mutant *KRAS* peptide vaccine in pancreatic cancer (10). However, most cancer vaccines thus far have demonstrated minimal clinical benefit due to immune suppressive mechanisms; until the option of an immune checkpoint inhibitor blockade as companion therapy became evident. New combination cancer vaccine trials, such as the upcoming MYPHISMO trial (NCT03287427) targeting colorectal and adenoid cystic carcinomas and TG02 trial

(NCT02933944) aimed at mutant KRAS, will be crucial in advancing this mode of treatment (11).

As the primary recipient of most solid cancer referrals, surgeons have the unique opportunity to recognise and consider immunotherapy as an extension of their surgical armamentarium. With the push for personalised cancer care, tumour molecular and immune profiling is coming to the fore with the extension of immunotherapy as the fourth pillar in cancer treatment after surgery, chemotherapy and radiotherapy. Therefore, the potential scenarios for surgical-immunotherapy are genuinely exciting, as suggested below.

For early stage disease, the obvious choice is curative resection followed by adjuvant immunotherapy to reduce the risk of recurrence. In patients with locally advanced disease with threatened margin, neo-adjuvant immunotherapy can be utilised to downstage the disease and potentially allow for a R0 resection; with the option of adjuvant immunotherapy.

In cases of loco-regional disease, an immunotherapy 'sandwich' may be the best choice with immunotherapy given initially into an antigen-rich environment to aid in priming, followed by surgical debulking to enhance immunotherapy efficacy through disease burden reduction, and then backed-up with 'booster' immunotherapy.

Surgery still has a role in metastatic disease to debulk as well as harvest lymphocytes for adoptive cellular therapy, i.e. metastasectomy.

Whether utilised as primary or adjunctive therapy, immune-based therapies will undoubtedly improve surgical and oncological outcomes. Surgeons should embrace it as a new tool in the fight against cancer and facilitate further research in this field.

In conclusion, there is no definitive answer to our titular question, however surgical oncology is likely to remain a central pillar of cancer management, with immunotherapy becoming a fourth pillar for the management of cancer patients.

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