PERSPECTIVE

Royal Australasian College of Surgeons

Theranostics: a fifth pillar of contemporary cancer care?

Cancer is a leading cause of mortality in Australia, with approximately 151 000 new diagnoses and 49 000 cancer-related deaths in 2021.[1] The oncological 'pillars' of surgery, chemotherapy and radiotherapy are being augmented by targeted molecular therapies and immunotherapy and the distinction between curative-intent and palliative-intent treatments has become blurred, as more and more patients live with cancer as a chronic condition, moving between treatment modalities as required. As the focus on personalized oncology intensifies, surgeons must understand each pillar of cancer care, and how they can be used as alternatives or adjuncts to surgery. Theranostics is an important modality with an established and expanding role in cancer care, but which has not traditionally been considered an oncological pillar. This article highlights the increasing significance of theranostics across many different malignancies.

'Theranostics'—a portmanteau of 'therapeutics' and 'diagnostics'—was first used in the 1990s to refer to radioimmunotherapy, and subsequently has encompassed all types of targeted conjugate treatments. Theranostics utilizes a molecule (e.g., monoclonal antibody) that localizes and attaches to a cellular marker present exclusively or predominantly on diseased cells to deliver a conjugate pharmaceutical for imaging and/or treatment. For diagnostic imaging, the conjugate is usually a radionuclide that emits gamma radiation (e.g., ^{99m}Tc or ^{123}I) or positrons (e.g., ^{68}Ga or ^{18}F), detectable by single photon emission computed tomography (SPECT) or positron emission tomography (PET). This provides radiological localisation of targeted cells. For therapy, the targeting molecule is attached to a cytotoxic payload—most commonly a radioactive isotope (typically a beta emitter, e.g., ^{177}Lu or ^{131}I), or a chemotherapeutic or thermogenic agent. Effective theranostic treatments require the target molecule to be expressed consistently throughout cancer tissue. Typically, a 'theranostic pair'—two conjugates used serially to target the same marker, one for localisation or staging, and the other for selective destruction of target cells—are used in tandem to plan and execute treatment, and then to assess response and monitor for progression.

Theranostics began when radioactive iodine ('RAI') was developed to treat differentiated thyroid carcinoma in 1946. RAI (^{131}I) targets the sodium/iodine symporter found exclusively in follicular thyroid cells. ^{131}I emits low-energy gamma rays that are detectable with diagnostic scintigraphy to localize residual or metastatic thyroid tissue *in vivo* following thyroidectomy. At higher doses, its beta emissions are lethal to residual thyroid cells. RAI is demonstrated to improve recurrence rates and survival following thyroidectomy in patients with high-risk differentiated thyroid malignancies and has been used for many years.[2]

The theranostic niche widened in the 1980s and 1990s with the evolution of bone-seeking radiopharmaceuticals for management of osteoblastic bone metastases, as well as the development of radioiodinated metaiodobenzylguanidine (MIBG) and peptide receptor radionuclide therapy (PRRT) for management of various neuroendocrine tumours (NETs). Bone-seeking theranostics (such as ^{89}Sr), which structurally mimic calcium and are taken up by osteoblastic lesions, were developed in the 1940s but widely adopted as palliative therapy for disseminated bone metastases following phase 3 trials in the 1990s.[3] MIBG is a noradrenaline analogue that is taken up selectively by neural crest-derived NETs, including paediatric neuroblastoma, phaeochromocytoma, and medullary thyroid cancer. ^{123}I- or ^{131}I-labelled MIBG is used similarly to RAI.[4] PRRT targets the somatostatin receptors expressed on many gastro-entero-pancreatic NETs using somatostatin analogue (SSA)-based radionuclide conjugates for PET imaging (e.g., ^{68}Ga-DOTA-SSA) and targeted treatment (e.g., ^{177}Lu-DOTATATE).[5] Due to the relative rarity of NETs and the dominance of surgery in their treatment algorithm, historically these technologies were used predominantly for diagnosis and staging. Their therapeutic applications were utilized selectively (and inconsistently) in patients with advanced disease, until the NETTER-1 trial was published in 2017.[6] This was the first large, phase 3 randomized controlled trial of a theranostic treatment for an otherwise surgical disease. It demonstrated patients with inoperable midgut NETs treated with ^{177}Lu-DOTATATE plus standard of care octreotide had significantly longer progression-free survival (PFS) compared with octreotide alone. As a result, PRRT is now accepted second-line therapy for well-differentiated, inoperable NETs.

The utility of theranostics has become topical with the development of prostate specific membrane antigen (PSMA)-based theranostic agents for metastatic prostate cancer. PSMA is a protein present on all prostate cells, with increased expression in prostatic adenocarcinoma and minimal physiological expression on non-prostate cells, making it a highly suitable theranostic target.[7] Several high-affinity PSMA-targeting imaging compounds have been developed, with ^{68}Ga-PSMA-11 PET/CT increasingly being used in place of conventional imaging in the staging of both high-risk primary and metastatic/recurrent prostate cancer since the publication of the ProPSMA trial in 2020.[8] Increasingly, PSMA-targeted therapeutic agents are also emerging from the trial phase into the clinic. The landmark phase 3 randomized open-label VISION trial of ^{177}Lu-PSMA-617, a PSMA-targeting small molecule conjugated to a cytotoxic beta-emitting isotope of lutetium, plus standard of care in castrate-resistant metastatic prostate cancer demonstrated

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significantly improved radiographic PFS and overall survival compared with standard of care.[9] The Australian randomized phase II TheraP trial of ^{177}Lu-PSMA-617 further demonstrated improved PFS compared with chemotherapy.[10] These results make it likely that ^{177}Lu-PSMA-617 therapy will become a standard treatment for metastatic castrate-resistant prostate cancer.

The longstanding utilization of RAI, as well as the recent success of large prospective trials of both PRRT and ^{177}Lu-PSMA-617 therapy, demonstrate that theranostics has a genuine role to play in the management of many solid cancers. Research into theranostics is extensive, with novel cellular targets being identified, including markers expressed across multiple cancer types that might potentially be targeted by tumour-agnostic theranostics. Innovative radionuclides are being developed for imaging and therapy, and paradigm-shifting nanoparticles have been engineered that can target and kill malignant cells through their intrinsic chemical and physical properties. The future of cancer care is personalized programs of therapy, bespoke to the individual molecular tumour characteristics. Theranostics will likely become a key pillar of treatment for cancer patients in this new oncological landscape.

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