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Know thy tumour: Biomarkers to improve treatment of molecular radionuclide therapy

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ABSTRACT

Molecular radionuclide therapy (MRT) is an effective treatment for both localised and disseminated tumours. Biomarkers can be used to identify potential subtypes of tumours that are known to respond better to standard MRT protocols. These enrolment-based biomarkers can further be used to develop dose-response relationships using image-based dosimetry within these defined subtypes. However, the biological identity of the cancers treated with MRT are commonly not well-defined, particularly for neuroendocrine neoplasms. The biological heterogeneity of such cancers has hindered the establishment of dose-responses and minimum tumour dose thresholds. Biomarkers could also be used to determine normal tissue MRT dose limits and permit greater injected doses of MRT in patients. An alternative approach is to understand the repair capacity limits of tumours using radiobiology-based biomarkers within and outside patient cohorts currently treated with MRT. It is hoped that by knowing more about tumours and how they respond to MRT, biomarkers can provide needed dimensionality to image-based biodosimetry to improve MRT with optimized protocols and personalised therapies.

Contents

1. Introduction

Molecular radionuclide therapy (MRT) involves the injected delivery of radionuclides that decay and release ionising radiation within the patient, preferably within target lesions such as malignant tumours. For this reason, MRT is sometimes referred to as targeted radionuclide therapy (TRT), or radiopharmaceutical therapy (PRT) as it typically uses the natural biological affinity of the radionuclide itself in the case

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of [^{131}I]NaI, or it is covalently appended to a biological mimetic such as ^{131}I-metaiodobenzylguanidine [^{131}I]mIBG or coordinated to a peptide with biological affinity for a surface receptor in the case of lutetium-177 tyrosine-3-octreotate [^{177}Lu]Lu-DOTATATE. This elevated uptake in target lesions over normal tissue can be by increased expression of membrane transporters such as the sodium iodide symporter in thyroid cancers for [^{131}I]NaI therapy, or elevated expression of receptors such as somatostatin receptor 2 for the somatostatin analogue [^{177}Lu]Lu-DOTATATE. These targeted therapies can boast impressive improvements to both survival and quality of life over conventional non-radiation treatments, as seen in the relatively recent phase III NETTER-1 trial results in 2017 for midgut neuroendocrine tumours (NET) with [^{177}Lu]Lu-DOTATATE [1]. Despite being generally well tolerated, the objective response rate of this therapy remains around 15–35% [2]. To improve this response rate, increasing the number and/or injected activity from the standard dose of 7.4 GBq every 6–8 weeks could achieve this outcome, but it could also unnecessarily overtreat and increase normal tissue toxicity in patients, particularly those that may already be well suited to the standard dose regime. This is still an ongoing dilemma for radioiodine therapy for thyroid cancer despite an 80 year head-start [3]. It is established that high-risk thyroid patients benefit well from high dose [^{131}I]NaI ablation of the remnant tissue following surgical resection [4]. However, the ideal dose given to low-to-medium risk patients is less certain and remains controversial given the lack of sufficiently long-term prospective clinical trials (>10 years) to assess the incidence of secondary neoplasms [5]. Biomarkers can be used by clinicians to assess risk and traditionally biomarkers have been classified as either prognostic or predictive biomarkers. In this case prognostic biomarkers, providing information about the patient's overall outcome regardless of therapy would inform the urgency of intervening in high-risk thyroid cancer with the extent of surgical resection and radioablation, or in lower risk patients' surgical resection may be sufficient [5]. Whether or not radioablation is necessary is currently being assessed in two large prospective trials, IoN trial (NCT01398085) and ESTIMABL2 (NCT01837745). Predictive biomarkers would provide information about the therapeutic effect of the radioiodine treatment itself [6]. These biomarkers include SPECT/PET image-based uptake measurements and biological signatures (including genetic, epigenetic or proteins) analysed from biopsies of both blood and tumour from patients. These biomarkers are usually developed for each MRT agent and tailored to the distinct cancer biology of each target malignancy. When considering the pragmatic use of biomarkers of MRT they can be separated to achieve two different outcomes:

1. Enrolment biomarkers in the clinic to include or exclude patients for courses of MRT using established protocols
2. Radiobiology biomarkers to improve or establish new MRT protocols.

Enrolment biomarkers of the more recent MRT agents such as [^{177}Lu]Lu-DOTATATE have focused on identifying the most suitable patients for MRT enrolment, and have been extensively reviewed elsewhere [7,8]. These biomarkers can threshold the 'responders' from 'non-responders' according to the standardised dose regime proven to work in cohort-based clinical trials and indeed is one of the reasons for the relatively rapid progression and success of these trials. While this segregation between 'responders' and 'non-responders' with predictive biomarkers is typical for chemotherapy drug protocols, it doesn't have to remain the case for MRT because of the unique ability to visualise the distribution of the radiolabelled drug and therefore the radiation absorbed dose delivered within each patient [9]. The correlation of calculated absorbed doses with suitable biomarkers could account for the spectrum of response across all patients, not just responding and non-responding cohorts. Radiobiology biomarkers have the potential to not only improve existing MRT by understanding how normal tissues respond to these different sources of ionising radiation but also account for the uncertain biology of tumours. This mini-review will discuss how both enrolment and radiobiology biomarkers can be used to improve molecular radionuclide therapy. Furthermore, we will argue that radiobiology biomarkers should not be considered a competitor to dosimetry, but rather a necessary complement to dosimetry in order to address the biological uncertainty of tumours.

2. Enrolment biomarkers

There are various biomarkers developed to identify patients that would benefit most from enrolment to MRT. While enrolment is a term usually used for patient selection of clinical trials, it is used here to emphasise the legacy clinical trial design on MRT such as [^{177}Lu]Lu-DOTATATE. The protocol used in NETTER-1 has largely remained fixed within the clinic at 7.4 GBq of [^{177}Lu]Lu-DOTATATE every 6–8 weeks. In order to increase the response rate of a MRT such as [^{177}Lu]Lu-DOTATATE either the protocol could change and adapt, or you could bias the selection of patients to cohorts that are known to respond. There are efforts to identify and understand the relatively distinct subtypes of thyroid cancers, pheochromocytoma and paraganglioma (PPGL), neuroendocrine and neuroblastoma using biomarkers (Fig. 1). By identifying these distinct subtypes by solid biopsy, MRT can be adapted to each tumour subtypes. However, due to the inherent biological heterogeneity of neuroendocrine neoplasms no distinct subtypes have been identified by individual biomarkers, instead a multianalyte approach has been used. Potentially the most impactful enrolment based biomarker for MRT is the use of diagnostic analogues of MRT agents themselves. Patients demonstrating sufficient tumour uptake using these diagnostic agents as detected by PET/SPECT is a typical enrolment criteria for MRT clinical trials and so remain an enrolment biomarker within the clinic.

2.1. Enrolment biomarkers for distinct genetic tumour subtypes

Tumour biopsies are regularly acquired in many cancers treated with MRT, typically at earlier stages of diagnosis and treatment before courses of MRT. Neuroendocrine tumours are primarily staged by the proliferation marker Ki-67 *ex vivo* with tumour biopsies to index the number of dividing cells. Grade 1 neuroendocrine neoplasms (NEN G1) have a Ki-67 index of <2%, NEN G2 between 3 and 20%, and greater than 20% is classed as grade 3 neuroendocrine carcinoma (NEC G3). NEC are phenotypically more aggressive and have a much poorer prognosis [10]. Critically, NEC were considered 'non-responders' to [^{177}Lu]Lu-DOTATATE treatment due to their poor prognosis and typically low expression of sstr2 receptors, but there is recent efforts to expand the enrolment of these patients with MRT [11].

Histopathological features of suspected thyroid cancer biopsies combined with other clinical factors such as age and presence of metastasis can provide reliable prognostic scoring of thyroid cancer [12]. Common genetic mutations belonging to the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase/protein kinase B (PI3KCA/AKT) pathways including serine/threonine-protein kinase B-Raf (BRAF) mutations can serve as predictive biomarker of patients who are refractory to radioiodine therapy [13]. The enrolment of patients with this genetic subtype to receive MAPK inhibitors has been shown to restore radioiodine uptake [14,15].

The use of genetic sequencing of tumour biopsies has recently transformed the study of PPGL. Unlike most cancers treated with MRT agents, PPGL has one of the highest incidence of hereditary-linked somatic germline mutations of any cancer and recent genetic phenotyping has identified 3 distinct genetic clusters [16,17]. Currently, the only FDA approved treatment for PPGL is the MRT agent [^{131}I]mIBG based upon the sufficiently impressive results of a phase II clinical trial [18]. Although retrospective analysis is underway, this study was commissioned before the impact of these genetic subtypes was fully appreciated, particularly succinate dehydrogenase complex iron sulfur subunit B (SDHB). It is now apparent that each genetic cluster has its own molecular

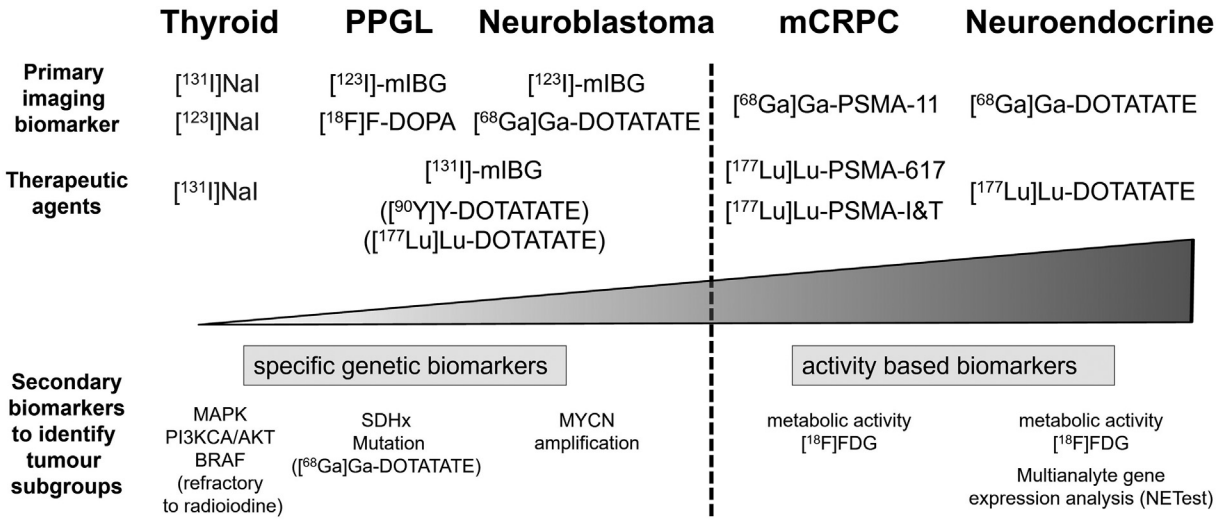

Fig. 1. Primary imaging biomarkers used in MRT patient enrolment and associated therapeutic MRT agents. Secondary biomarkers have also been used to identify tumour subtypes with different MRT response profiles. The increasing biological heterogeneity of metastatic castrate resistant prostate cancer (mCRPC) and neuroendocrine tumours is a challenge for the identification of specific tumour subtypes and instead metabolic activity and genetic expression profiles have been used.

phenotype that is reflected in the most optimal molecular imaging agent [19]. Choice of imaging agent impacts the ability to detect potentially resectable metastases and potential MRT agent to treat non-resectable metastases. For example PPGL with SDHx gene mutations can have higher expression of sstr2 and therefore have been investigated for therapy with [^{90}Y]Y-DOTATATE [20]. Whether to undertake genetic sequencing in suspected PPGL before or after molecular imaging in the clinic is still under debate [21].

After preliminary biomarker screening of the urine and serum, the tumour histopathology and genetic landscape of neuroblastoma is investigated using biopsy tissue [22]. One of the critical prognostic genetic biomarkers is the extent of MYCN amplification being reported in 25% of neuroblastoma patients and 40% of high-risk patients [23,24]. While these genetic screens are still ongoing, the image-based biomarker mIBG has been widely adopted as the standard for staging [25], and the overlap between genetic and imaging markers will be discussed later.

2.2. Enrolment biomarkers with non-distinct tumour subtypes

In the case of NET, the genetic and phenotypic landscape is much more diverse than PPGL as there isn't any single underlying genetic marker that can reliably identify why certain NET patients respond to therapy and others do not. Instead numerous potential genetic signatures have been identified by analysing a diverse set of genetic markers in known 'responders' [7]. The NETest is a multianalyte assay that identifies clusters of circulating gene transcripts out of 51 gene markers that were identified by network analysis of a GEP-NEN gene co-expression network to be associated with various forms of NET tumours [26]. These genes include transcripts for transport and metabolism, and sstr receptors but interestingly excluding sstr2 the primary somatostatin receptor used for DOTATATE uptake. While the NETest, and in conjunction with the PRRT prediction Quotient (PPQ) which tests eight circulating gene transcripts involved in the regulation of growth factor signaling and metabolism, is accurate in identifying 'responders' to the standard protocol treatment, it is also capable at monitoring when 'responders' become 'non-responders', in 97% of cases [27]. Despite showing great promise, it would be challenging to entirely replace [^{68}Ga]Ga-DOTATATE for qualifying patients for MRT enrolment as even if there is not significant tumour control, the quality of life improvements still do warrant giving MRT for sufficiently [^{68}Ga]Ga-DOTATATE-avid NET patients. However, NETest is able provide earlier detection of progression-free status than standard [^{68}Ga]Ga-DOTATATE imaging which is most reliable 3 months after the last round of PRRT [2]. Despite the earlier opportunity for clinical management change for these newly non-responding patients there is not yet any established alternate treatment protocol with [^{177}Lu]Lu-DOTATATE. Some alternate treatment possibilities being explored include alpha emitters [28], combination therapies [29], or chemotherapies alone. Since the biological landscape of NET tumours is so heterogenous, it may be necessary to apply this multianalyte biomarker approach to these 'non-responders' to standard protocols who become 'responders' using these alternate therapies for NET, and therefore provide future patients the opportunity to enrol alternate treatments tailored to their genetic transcript signature. It is encouraging that at least one new alternate treatment is using the NETest in their clinical trial treatment protocol [30].

2.3. Enrolment based upon image-based biomarkers

Diagnostic isotope analogues of MRT agents are used to determine if their uptake and expression of target surface receptors/channels is sufficient for subsequent MRT. This is the basis of theragnostics: 'you can treat what you can see'. These thresholds for treatment are typically either quantitative measurements such as standard uptake values including SUV_{max}, semi-quantitative metrics such as the Krenning score in the case of [^{68}Ga]Ga-DOTATOC or [^{68}Ga]Ga-DOTATATE imaging of NET and the extent of tumour burden has some predictive correlation with treatment outcome [31]. Although a powerful tool for diagnosis and to identify sites of NET metastases, accurate assessment of treatment-related morphological changes with [^{68}Ga]Ga-DOTATATE are of acceptable reliability only after 3 months post cessation of [^{177}Lu]Lu-DOTATATE therapy [2], and are therefore not a suitable basis for developing adaptive treatment protocols. Imaging biomarkers such as [^{68}Ga]Ga-DOTATATE can also provide some insight into the underlying biological character of each tumour and therefore stratify patients for MRT and that hopefully would be more tailored to the underlying tumour subtype. For example in NET, the expression of sstr2 is inversely correlated with NET grade, and with the more aggressive NEC carrying TP53 and RB1 mutations [32,33]. In addition, many of these de-differentiated tumours with reduced sstr2 expression and hence reduced [^{68}Ga]Ga-DOTATATE can be visualised by increased uptake of 18-fluorodeoxyglucose [^{18}F]FDG PET. NET patients with this discordant low [^{68}Ga]Ga-DOTATATE but [^{18}F]FDG-avid tumours have been found to have a significantly worse PFS (21.1 *vs* 68.7 months with patients with non-[^{18}F]FDG-avid tumour lesions at baseline) [34]. There have been encouraging results from a phase II trial treating [^{18}F]FDG-avid and low [^{68}Ga]Ga-DOTATATE

subtype NET patients with a [^{177}Lu]Lu-DOTATATE combination with capecitabine, with a phase III trial underway [35].

For metastatic castrate resistant prostate cancer (mCRPC) lutetium-177 Prostate Specific Membrane Antigen [^{68}Ga]Ga-PSMA-11 has been shown to be a superior imaging biomarker than the conventional radiological imaging techniques of CT and bone scanning in the recent phase III proPSMA trial [36]. [^{68}Ga]Ga-PSMA-11 had far greater accuracy than conventional imaging (92% *vs* 65%), and higher sensitivity (85% *vs* 38%), and specificity (98% *vs* 91%). Critically, [^{68}Ga]Ga-PSMA-11 imaging resulted more frequent changes to clinical management 41% *vs* 23%, and even resulted in less radiation exposure than conventional imaging techniques (8.4 mSv *vs* 19.2 mSv). [^{68}Ga]Ga-PSMA-11 also can be used to determine whether a patient would be eligible for [^{177}Lu]Lu-PSMA-617 treatment, with the whole-body tumour [^{68}Ga]Ga-PSMA-11 SUV_{mean} appearing to be the most promising metric that correlates with mean absorbed dose ($r = 0.62$) [37]. Although not necessarily equivalent with overall survival, a 50% serum Prostate Specific Antigen (PSA) decline was observed in patients with a median dose of 14.1 Gy *vs* 9.6 Gy for those achieving a PSA response of <50% and therefore dose calculations based upon [^{68}Ga]Ga-PSMA-11 uptake could be foreseeably used to determine patient enrolment for [^{177}Lu]Lu-PSMA-617 treatment. However, the use of metrics like whole body SUV_{mean} have been used to accommodate the heterogenous uptake and expression of PSMA within each patient. Dual tracer imaging with [^{18}F]FDG has been adopted for mCRP in a similar way for NET, and has been used to determine the eligibility and prognosis of patients for [^{177}Lu]Lu-PSMA-617 [38]. The exclusion of 'non-responder' patients with any [^{18}F]FDG-avid and non-avid [^{68}Ga]Ga-PSMA-11 tumours appear to result in greater efficacy compared to other clinical investigations [39]. While it is possible that [^{177}Lu]Lu-PSMA-617 could have provided some therapeutic or even palliative benefit to these excluded patients, without treatment their outcome was very poor, with a mean overall survival of only 2.5 months (95% confidence interval 1.7–5.0) [40]. All excluded patients that received an [^{18}F]FDG scan (15 out of 16 patients) had discordant tumours with elevated [^{18}F]FDG with varying levels of [^{68}Ga]Ga-PSMA-11. Despite the high patient incidence of elevated [^{18}F]FDG, this is not a common feature of prostate cancers [41], and elevated levels are independently known to give a poor prognosis for mCRPC [42,43]. Interestingly, in a case study when using both [^{18}F]FDG/[^{68}Ga]Ga-PSMA-11 in a patient who biochemically progressed after 2 rounds of [^{177}Lu]Lu-PSMA, revealed [^{18}F]FDG-avid [^{68}Ga]Ga-PSMA-11-low tumours, and furthermore these lesions were positive for fibroblast activation protein inhibitor (FAP) using a FAP imaging (FAPI) biomarker [^{68}Ga]Ga-FAPI-04 PET/CT [44], presenting the possibility of FAPI being an additional biomarker or even theranostic possibility for these discordant 'non-responding' mCRPC tumours. FAP is a type II membrane bound serine protease belonging to the dipeptidyl peptidase 4 family that is highly expressed on cancer-associated fibroblasts [45], and is involved in remodelling of the tumour microenvironment including digestion, invasion and subsequent migration of tumour cells [46]. FAP has gained much attention recently for its potential as a pan-tumour imaging biomarker with broad applicability across a wide array of can [47], with many attractive qualities over the current pan-tumour imaging biomarker [^{18}F]FDG, including greater performance with distant metastases and patients not requiring fasting [48]. It is possible that the increased [^{68}Ga]Ga-FAPI uptake in these 'non-responding' tumours could be a result of increased cancer fibroblast associated radioresistance affecting the effectiveness of [^{177}Lu]Lu-PSMA treatment [49].

There are a number of potential imaging biomarkers used for assessing PPGL apart from [^{123}I]mIBG, including [^{68}Ga]Ga-DOTATATE, [^{18}F]FDG and ^{18}F-dihydroxyphenylalanine ([^{18}F]F-DOPA). If the genetic subtype is unknown, PPGL detection rate is 93% with [^{68}Ga]Ga-DOTATATE, 93% for [^{18}F]F-DOPA, 74% [^{18}F]FDG and 38% for [$^{123/131}$I]mIBG scintigraphy [50]. However, if the genetic subtype cluster is known, then these success rates do improve [19,50], and apart from properly assessing surgical options, patients can be enrolled with the most suitable MRT agent. For example, if patients have a SDHx gene mutation and sufficient uptake of [^{68}Ga]Ga-DOTATATE then the option of [^{90}Y]Y-DOTATATE is being explored [20]. Although there are relatively small numbers of patients with PPGL which would normally hamper MRT investigations like these, it is more likely if patient enrolment is based upon the combined use of genetic and imaging biomarkers such as these.

Neuroblastoma like PPGL is primarily assessed with [^{123}I]mIBG scintigraphy using the Curie scoring system [51], and treated with [^{131}I]mIBG, with even greater sensitivity 83–92% and specificity 88–92% at staging [52], and can provide a prognostic indicator of patients with high-risk neuroblastoma [51]. As in the case of PPGL sstr2 is also expressed in neuroblastoma, 77–89% of neuroblastoma cells by *ex vivo* analysis [52]. Although there is limited prospective data on using [^{68}Ga]Ga-DOTATATE, one study found greater sensitivity with [^{68}Ga]Ga-DOTATOC (97.2%) than [^{123}I]mIBG (90.7%) on a per-lesion basis [53]. Interestingly in this head-to-head comparison, [^{123}I]mIBG had a much lower sensitivity in PPGL (63.3%) than [^{68}Ga]Ga-DOTATOC (91.7%). Alternatively, [^{18}F]F-DOPA can be used to monitor the metabolism of catecholamines within neuroblastoma and has a high sensitivity of 97.6% and specificity of 87.5% [54], but it is challenging to synthesise, and therefore not as widely available [55]. Another upcoming PET-CT based biomarker is ^{18}F-meta-fluorobenzylguanidine [^{18}F]mFBG, which was able to detect all 63 lesions detected on [^{123}I]mIBG imaging (scintigraphy and SPECT-CT) and 59 additional lesions in a small mixed cohort of PPGL and neuroblastoma patients [56]. Unlike most other MRT treated cancers reviewed here, [^{123}I]mIBG non-avid neuroblastoma tumours (8.7%, 30 out of 343 patients) actually may have a better prognosis than avid tumours patients despite being more likely to have MYCN-amplified tumours [25]. It is recommended to use [^{18}F]FDG to assess and provide a prognosis of these [^{123}I]mIBG non-avid tumours despite normally being considered inferior in neuroblastoma evaluation [52]. Enrolment of patients for DOTATATE based MRT could be a potential treatment strategy [57], but as some patients present with discordant tumours taking up [^{123}I]mIBG and not [^{68}Ga]Ga-DOTATATE and *vice versa* suggests the potential of [^{177}Lu]Lu-DOTATATE and [^{131}I]mIBG combination treatment [58]. Alternatively in patients who were refractory or have relapsed after therapy with [^{131}I]mIBG but have high uptake of [^{68}Ga]Ga-DOTATATE, combined treatment with [^{177}Lu]Lu-DOTATATE and chemotherapy shows promise with low MRT related toxicity [59].

The threshold for enrolment of thyroid cancer patients for MRT remains controversial [60]. It is hampered by a lack of prospective randomised clinical trials leaving recommendations to be made based upon mainly retrospective analysis using single-site data with diverse surgical and interventional management [4]. There are still many lessons that can be learnt from using [^{123}I]NaI scintigraphy for initial patient dose-optimisation of [^{131}I]NaI therapy will be discussed in the following sections. For patients who are refractory to [^{131}I]NaI MRT, alternate imaging biomarkers are being explored that are worth highlighting that may provide alternate MRT-based treatment strategies. Incidental uptake of [^{68}Ga]Ga-DOTATATE in the thyroid was observed in 11% of patients being investigated for potential neuroendocrine tumours with 21% of these patients subsequently being found to have papillary thyroid cancer [61]. A recent preliminary investigation into [^{177}Lu]Lu-DOTATATE therapy was explored in 5 patients who were sstr2 positive and refractory to [^{131}I]NaI therapy [62]. Seemingly not be left out, [^{68}Ga]Ga-PSMA-11/[^{177}Lu]Lu-PSMA-617 therapy has also been similarly investigated for these same radioiodine refractory patients with a modest temporary response in one patient [63]. Here [^{68}Ga]Ga-PSMA-11 could detect lesions not identified by [^{18}F]FDG, but elsewhere it has been shown to perform worse [64], but the utility of [^{68}Ga]Ga-PSMA-11 should be investigated further as it could be more effective in patients with dedifferentiated thyroid cancer. The limited therapeutic activity may be due to the PSMA expression being found on the

neovasculature of the thyroid carcinomas rather than the tumour cells of prostate carcinomas [63].

3. Biomarkers for dose optimisation

Biomarkers such as SPECT/PET imaging agents could be used not just to enrol patients, but also to determine and calculate the necessary injected doses for patients. This dose optimisation is not necessarily a simple process, and it is helpful to consider the two different dosimetry-based approaches that have been applied to radioiodine therapy, as high as safely administrable (AHASA) and as low as reasonably achievable (ALARA) [65]. The AHASA approach is based upon the concept of one maximal therapeutic dose rather than smaller administered doses within the repair capacity of the tumour [66]. While this approach is limited by the maximum threshold of 2 Gy to the blood as a proxy for red bone marrow, it may very well be overtreating the tumour for which the ALARA approach's concept is to provide the minimal necessary absorbed dose (determined empirically in cohort studies) to ensure treatment to the primary tumour (300 Gy) and metastatic disease (80 Gy) [67]. This dosimetry-based approach alone for determining a dose-response in thyroid cancer cannot be assumed to also apply to other cancers treated with MRT. There remains a role for biomarkers to enrich dosimetry either to identify tumour subtypes (see Section 1) and enable cohort based dose-response calculations; or when tumour cohorts are unclear radiobiology-based biomarkers could provide insight into the tissue level dose response. Radiobiology-based biomarkers can be used alongside dosimetry to further understand normal tissue toxicity to refine AHASA thresholds for each MRT agent, as well as determine ALARA minimum necessary dose thresholds.

3.1. Biomarkers of normal tissue toxicity

There are currently no effective biomarkers for predicting normal toxicity inflicted by MRT [7], and as a result acceptable radiation absorbed dose limits for organs-at-risk have been set based upon those for external beam radiotherapy (EBRT). There are significant differences between the dose-rate and radiation absorbed doses of EBRT *vs* MRT, not only affected by the distribution of MRT agents within each organ such as the kidneys, which is largely the peripheral cortex with [^{177}Lu]Lu-DOTATATE [68], but also within each individual cell. It is much like comparing the impact of a sudden earthquake upon a house to that of a toddler in a COVID-19 lockdown house – that although the damage is more uniform in an earthquake, an ill-placed toddler will wreak havoc over time and by shear exhaustion of a continued repair response will cause the nucleus of the cell to be overwhelmed and lose its mind and likely become senescent upon the couch.

For example the current radiation absorbed dose limits for MRT for kidneys has been long criticised for being too conservative [69], and if treatment is pushed to the current 23 Gy limit of kidneys set from EBRT dose limits in a AHASA-manner, then a 1.48-fold dose to the tumour is predicted over standard treatment protocols [70], which could significantly increase overall survival [71]. There is evidence that even a 40 Gy biologically equivalent radiation absorbed dose is tolerated if certain renal risk factors are taken into consideration [72].

While there is currently no significant evidence of renal toxicity with current treatment protocols with [^{177}Lu]Lu-PSMA-617 therapy [73], there is concern for xerostomia as a result of significant radiation absorbed dose to the salivary glands [74], particularly with targeted alpha therapy using [^{225}Ac]Ac-PSMA-617 [75]. Although grade 3/4 xerostomia is relatively rare below a radiation absorbed dose of 50 Gy with MRT, the nature of this dysfunction is not completely understood [74], and additional research and biomarkers are needed to understand the dose-effect relationship of salivary gland toxicity with MRT and how it may potentially be different from EBRT {Taïeb, 2018 #65} [76]. [^{68}Ga]Ga-PSMA-11 revealed detected large inter-patient and even intra-patient variability, with cases of asymmetric dysfunction in those previously treated with radioiodine therapy [77]. Since xerostomia appears to occur as a result of numerous rounds of MRT [74], it would be prudent to identify patients at risk of developing xerostomia given the impact on the patient's quality of life. There are efforts to understand how radiotherapy on head and neck cancer patients affects baseline salivary gland function using MRI [78] and saliva biomarkers [79], but these techniques have not yet been applied to mCRPC patients receiving [^{177}Lu]Lu-PSMA. Indeed due to its high affinity to salivary glands, there is interest in using [^{68}Ga]Ga-PSMA-11 alongside $^{99m}TcO_4^-$ salivary gland scintigraphy to assess salivary gland function more generally outside of prostate cancer [80]. However recent preclinical investigations with pig salivary glands suggest that uptake may be a combination of non-selective and non-selective uptake [81]. Imaging clinical trials using [^{68}Ga]Ga-PSMA-11 have been undertaken to investigate strategies to limit uptake in salivary glands. These include limited effects using cold compresses [82], and, more recently, monosodium glutamate (MSG) which although successful at decreasing uptake, also significantly decreased tumour uptake, potentially limiting the therapeutic benefit of this approach [83]. Another strategy that is worth noting is to regenerate salivary glands post radiation treatment using stem cell therapy that has shown promise in an early phase clinical trial [84].

Although not considered the main dose-limiting toxicity with standard treatment protocols of [^{177}Lu]Lu-DOTATATE or [^{177}Lu]Lu-PSMA-617, haematological toxicity may become significant with elevated or additional injected doses, or when assessing combination therapies. There are established minimum thresholds for patient haemoglobin, total white cell counts and platelet counts before each round of MRT as indirect markers of the bone marrow reserve [85]. Reduced bone marrow reserve in older patients (>70 years) is also commonly taken into consideration for determining the activity levels for radioiodine therapy for thyroid cancer [86]. One early study showed a dose-dependent effect of acute haematological changes and blood-based activity levels [87], but numerous other studies since have had difficulty correlating red marrow dose with haematological toxicity [69]. These variable results may be affected by the SPECT imaging and quantification method and by the presence of bone metastases [88]. The microscale dose distribution of MRT agents within the bone marrow can also be challenging to predict. Despite selective accumulation of $^{223}RaCl_2$ (Xofigo) within the bone, minimal grade 3 or 4 haematological toxic effects were observed including neutropenia (2%), thrombocytopenia (3%), leukopenia (3%) and pancytopenia (1%) [89]. This is attributed to the microscale distribution of Ra-223 dose to within 80 μm of the bone surface [90]. Despite the low incidence of haematological toxicity, the imaging biomarker fluorine-18-fluorocholine ([^{18}F]-FCH) has been shown to predict haematological toxicity in mCRPC patients treated with $^{223}RaCl_2$ [91]. Secondary myeloid neoplasms currently have an incidence of about 2.6% in NET patients treated with [^{177}Lu]Lu-DOTATATE and present relatively early (1–3 years post treatment) [92]. One biomarker that has been investigated to identify which patients are vulnerable to develop myeloid neoplasms or to establish a dose-threshold value is the measurement of phosphorylated histone H2AX variant (γH2AX) foci present within circulating peripheral blood of patients receiving MRT. Since γH2AX is largely accepted as a proxy marker for the presence of unrepaired DNA double strand breaks, the presence of γH2AX may be used to ascertain DNA damage in circulating leukocytes as a surrogate for DNA damage to the red pulp within the bone marrow [93]. The use of radiation induced γH2AX foci within peripheral leukocytes is not limited to the study of MRT and has been investigated in patients receiving external beam radiotherapy. Typically, γH2AX foci are counted, or the total level of γH2AX expression is determined, after extracted blood is irradiated *ex vivo*, to establish whether a patient is inherently more radiosensitive [94]. This variation in radiosensitivity is due to the large known inter-individual differences in DNA repair capacity [95]. The impact of haematological toxicity should be considered for each MRT agent as one recent study reported significant differences between patients receiving

[^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-DOTATATE that could not be simply accounted for by differences in radiation absorbed dose or dose-rate, despite having dose-dependent γH2AX foci within each MRT treatment group [96]. It seems rather unlikely that underlying differences in normal tissue radiosensitivity between NET and mCRPC patient groups would be this significant, but seemingly subtle differences in cellular distribution and uptake between these radionuclide agents may significantly impact the biological response and supports the need for further radiobiological investigation [97].

3.2. Challenges in establishing cohort based ALARA thresholds with MRT

Establishing an ALARA minimum cumulative injected dose required to elicit tumour regression can be a greater challenge than establishing limits of normal toxicity, depending upon the heterogeneity of the cancer type. As introduced previously, ALARA dose thresholds for thyroid cancer have been established for decades, with the primary tumour (300 Gy) and metastatic disease (80 Gy) [67]. In addition, for the treatment of neuroblastoma a tumour self-absorbed radiation dose (TSARD) using [^{131}I]mIBG correlated with overall disease response and tumour volume reduction, despite only using a conjugate planar method [98]. Using patient-specific dosimetry with more advanced three-dimensional tumour images has been used to tailor higher doses of [^{131}I]mIBG successfully in neuroblastoma [99], and development of standard operating procedures for [^{131}I]mIBG dosimetry [100]. These dose-response correlations with [^{131}I]mIBG have similarly been known for PPGL [101]. While it may seem that there is not actually any challenge in establishing dose-response thresholds for MRT, it really depends upon the biological identity of the cancer. The calculation of a relatively simple dose-response may be more of a reflection of a simpler biological tumour landscape with limited 'non-responding' outliers. If there is no dose-response it may be due to multiple unknown tumour subsets within the study's cohort, something that will remain unknown unless biomarkers can be used to segregate analysis. This segregation of unknown cohorts treated with MRT can be used with biomarkers such as those discussed in Section 1, such as patients with discordant [^{18}F]FDG-avid lesions in NET and mCRPC, and re-examination of PPGL genetic clusters. Practically this is more challenging as it would require dosimetry analysis of more patients to have statistically sufficient numbers within each sub-group, necessitating multi-centre dosimetry trials and therefore standardisation of SPECT/PET detectors and analysis. It is encouraging that these practical obstacles are being addressed with funded projects such as MEDIRAD project [102]. Other non-nuclear imaging biomarkers should not be overlooked, such as recent advancements with MRI diffusion weighted imaging MRI (MRI-DWI). Apparent diffusion coefficients with MRI-DWI have been associated with significant post-chemotherapy tumour reductions where [^{123}I]mIBG had no significant association [103]. While these studies have not yet been applied to [^{131}I]mIBG MRT, the association between diffusion and effective delivery of MRT agents such as [^{177}Lu]Lu-DOTATATE have been found preclinically [104,105]. Restricted perfusion by MRI is also known to be characteristic of more aggressive pancreatic NETs [106], and there are efforts to incorporate additional metrics such as tumour perfusion and receptor density with dosimetry to account for this biological heterogeneity to determine a more personalised tumour control probability [107].

The need for incorporating more biomarker metrics in dose-response calculations can be seen for the heterogenous tumour presentations of NET and mCRPC. While one SPECT imaging-based dosimetry study found a radiation absorbed dose-response with pancreatic NETs following [^{177}Lu]Lu-DOTATATE therapy [108], with improved correlation between radiation absorbed dose and tumour reduction found in tumours with a diameter greater than 4 mm. No radiation absorbed dose-response could be established for small intestine NET when applying the same imaged-based dosimetry technique [109]. The influence of lesion size and potentially differences in tumour microenvironment was reflected in the long-term analysis of the NETTER-1 trial, which found poorer outcomes for participants with at least one large lesion (>30 mm) [110]. This heterogeneity of tumours within patients is a common challenge affecting the application of image-based dosimetry for dose optimisation. Smaller and/or diffuse tumours are particularly challenging to segment and monitor during therapy, and is particularly problematic with PSMA-based MRT as found with [^{177}Lu]Lu-PSMA-I&T [111]. Various image-based metrics have been explored to account for this inter-lesion heterogeneity as standardised uptake volume SUV_{max} measurements with [^{68}Ga]Ga-PSMA-617 do not appear to correlated with therapeutic response [112]. Sufficient uptake in all lesions within a patient appear to respond best, and so measurements such as $SUV_{average}$ and $SUV_{minimum}$ may provide a better metric for future dose optimisation [113]. Similarly, a better predictor of poor treatment outcome is low expressing [^{68}Ga]Ga-PSMA-617 and [^{18}F]FDG-avid lesions [38], and upon excluding these non-responding patients one study [114], appeared to elicit a greater progression free survival with [^{177}Lu]Lu-PSMA based therapies compared to other studies [39], with a similar relationship for MRT with [^{177}Lu]Lu-DOTATATE [34]. Considering the likely biological differences in non-responding patients observed in these imaging studies, the heterogenous uptake and aggressive [^{18}F]FDG-avid phenotype, it may not be possible to easily aggregate these patients neatly within tumour subtypes to establish various radiation absorbed dose-responses without any characteristic biomarkers.

3.3. Radiobiology biomarkers

A different strategy to the enrolment-like approach of finding characteristic sub-cohorts with each calculated dose-response curve is to consider the dose-response curve within each patient. Ultimately the ALARA approach is to inject the necessary dose that is sufficient to treat the tumour, that is the dose given exceeds the capacity of the tumour to repair from the damage inflicted by MRT. Therefore, if the repair capacity of each patient could be determined with a biomarker of the repair response, then the necessary injected dose could be refined with each subsequent round of MRT. It is anticipated that this repair capacity approach would be more useful when the tumour biological landscape is more uncertain as with NET and mCRPC. While the repair capacity approach has not been directly investigated with MRT, the inter-individual spectrum of baseline radiosensitivity and repair capacity is known to affect both disease susceptibility and cancer treatment efficacy with EBRT [95]. Elevated DNA repair capacity has been found in numerous cancers including bladder [115], ovarian [116], colon [117], glioblastoma [118], and high risk prostate cancer [119]. In addition to genetic variation, differences in the tumour microenvironment and immune signaling have also recently been shown to affect the repair capacity of the tumour [120,121], as well as the availability of nucleotides to rebuild DNA in response to radiation [122]. Due to the collective contribution of all these factors in the extent and fitness of the DNA damage response, functional assays such as the comet assay [123] have been proposed as the most appropriate method to integrate the capacity of the DNA damage response rather than genetic screening alone [95], and this certainly aligns with the need for multiparametric approach with NET using the NETest. The Recombination CAPacity (RECAP) test is another functional assay that evaluates the DNA damage response following *ex vivo* irradiation of reconstituted biopsied ovarian tumours by detecting the presence of γH2AX foci and extent of RAD51 foci for reliable detection of defective homologous recombination (HR) [124]. This test was effective at determining the "BRCAness" defect that are known to be particularly sensitive to PARP inhibitor therapy including patients with no detectable breast cancer gene 1 and 2 (BRCA1/2) gene variants. Although the RECAP test employs the use of external beam radiotherapy as the source of DNA damage, this strategy of detecting *in situ* DNA damage response could also be applied to the monitoring of MRT. Another translatable approach to determine repair capacity in response to MRT is the fluorescence-based multiplexed host cell reactivation assay, which,

using 12 patient-derived glioblastoma xenografts, could predict survival and treatment resistance when measuring multiple DNA damage response pathways [118]. However, these approaches are limited by collection of tumour biopsies, which can be challenging to obtain, and may not fully capture the known inter- and inter-lesion heterogeneity in NET and mCRPC patients, suggesting that a non-invasive imaging approach may be more suitable. Furthermore, a comparison between *in vivo* and *ex vivo* irradiated tumour xenografts found significant differences in intra-tumoural distribution of γH2AX foci indicating the value of *in situ* measurement of the DNA damage response [125].

Imaging the damage response *in situ* to MRT is possible through radiolabelled molecular probes that target DNA damage repair proteins and enzymes indicative of the extent of the repair response. The DNA damage response resembles a complex orchestra, requiring a diverse set of instruments activated in correct sequence, rhythm, and tune achieve the correct ligation and repair of the DNA chain. Due to inherent sensitivity limits, imaging a repair associated protein with large copy number is desirable, that is, it is better to target the entire violin section rather than the single conductor regardless of how critical the conductor may be at directing the repair process. For this reason, imaging γH2AX is a desirable target, and we have recently demonstrated the ability to image the γH2AX damage response within a tumour treated with [^{177}Lu]Lu-DOTATATE *in vivo* using an indium-111 radiolabelled modified antibody [126]. Due to the desirable largely non-overlapping emissions of this isotope pair of lutetium-177 and indium-111, dual isotope SPECT imaging and analysis is possible to further understand the damage response to varying levels of MRT agents such as [^{177}Lu]Lu-DOTATATE in a tumour. One observation from the RECAP study is the universal expression of γH2AX foci in ovarian tumour samples in response to radiotherapy [124], underscoring the universal utility of this marker.

Normally, orchestras have a limited number of oboes, yet tumour cells can have an abnormal number of DNA repair instruments, providing them with the capacity to improvise and deal with any tricky DNA damage music inflicted by MRT. One such oboe is poly-ADP ribose polymerase (PARP) which has been found to have a role in all DNA repair pathways [127]. Even though there is twice the baseline expression of PARP in prostate tumours compared to normal tissue [128], in response to ionising radiation even more PARP oboes can be called upon to be packed into the woodwind section providing even greater repair capacity [129]. It is possible to image PARP preclinically and clinically with radiolabelled probes that are structurally similar or isotopologues of inhibitors of PARP [130]. There is evidence that in response to alpha emitting [^{225}Ac]Ac-PSMA-617 in a preclinical model there is increased uptake of one of these radiolabelled PARP inhibitors indicating an elevated damage response [131], increasing from days 1 to 6 post-treatment – packing the orchestra with either more or louder oboes. In addition to providing insight to the repair capacity of tumours against MRT, imaging of abnormal PARP expression could indicate patients suitable for potentially synergistic MRT combination therapies with PARP [132], with a clinical trial underway (NCT03874884). Therefore, although imaging the DNA damage response can provide insight of how much extra MRT dose is required to treat each tumour, they also provide an option to effectively cut the strings and reeds of the DNA response orchestra and even justify using less injected activity in each dose. These super-additive treatments could be achieved either through the use of "cold" PARPi with MRT, but also Auger emitting iodinated PARPi [133], and amplified with Indium-111 radiolabelled anti-γH2AX modified antibodies [134].

4. Conclusions

Biomarkers can provide much needed insight to improve MRT. They can serve to enrol patients to different MRT regimes based upon the identification of distinct tumour subtypes, especially in the case of PPGL. Absorbed dose-response relationships may be calculated within these defined tumour groups to establish minimum therapeutic doses. This is possible as ALARA thresholds have been achieved for radioiodine ablation of thyroid cancer. However, efforts to establish such thresholds for lower incidence cancers such as NENs have not been as successful. The biological heterogeneity of these cancers have precluded the use of simple biomarkers and instead multianalyte tests trained upon 'responder' patient cohorts have found greater success. While these multianalyte tests are powerful, they are limited to the promotion of specific MRT protocols in specific cancers and cannot be easily adapted. A more direct measurement of the treatment response to MRT with radiobiology based biomarkers could be a suitable strategy to accommodate the biological heterogeneity of cancers such as NENs and provided needed dimensionality to dosimetry calculations. We envision that the use of radiobiology-based biomarkers than just enrolment-based biomarkers, MRT protocols could be adapted to the patient rather than patients matched to the MRT.

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Given their role as Editor, Bart Cornelissen had no involvement in the peer-review of this article and has no access to information regarding its peer-review.

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Declaration of competing interest

The authors disclose no potential conflicts of interest.

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