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REVIEW

Incorporating prognostic imaging biomarkers into clinical practice

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Abstract

A prognostic imaging biomarker can be defined as an imaging characteristic that is objectively measurable and provides information on the likely outcome of the cancer disease in an untreated individual and should be distinguished from predictive imaging biomarkers and imaging markers of response. A range of tumour characteristics of potential prognostic value can be measured using a variety imaging modalities. However, none has currently been adopted into routine clinical practice. This article considers key examples of emerging prognostic imaging biomarkers and proposes an evaluation framework that aims to demonstrate clinical efficacy and so support their introduction into the clinical arena. With appropriate validation within an established evaluation framework, prognostic imaging biomarkers have the potential to contribute to individualized cancer care, in some cases reducing the financial burden of expensive cancer treatments by facilitating their more rational use.

Keywords: *Prognostic; hazard ratio; imaging biomarker; cancer; clinical practice.*

Introduction

A prognostic imaging biomarker can be defined as an imaging characteristic that is objectively measurable and provides information on the likely outcome of the cancer disease in an untreated individual. It is important to note the quantitative nature of imaging biomarkers, which places demands on imaging technologies that differ from those associated with the more familiar qualitative approaches that encompass much of clinical radiology. Prognostic biomarkers should be distinguished from predictive imaging biomarkers and imaging markers of response. Predictive imaging biomarkers are imaging characteristics that provide information on the likely benefit from treatment and are discussed in detail elsewhere in this journal[1]. Imaging biomarkers of response represent surrogate measures for the beneficial outcomes that are intended from treatment. These surrogates are useful either because they can be obtained at an earlier time point than the intended outcome or because they provide an alternative to assessment of pathologic response. Potential confusion and overlap between these terms can arise when the intended benefit from treatment being predicted or assessed is an improvement in survival.

Clinical tumour staging can be considered as a prognostic biomarker. However, it is increasingly recognized that patients with identical tumour stage can follow divergent clinical courses. Prognostic imaging biomarkers aim to further stratify risk beyond clinical stage. As indicated above, prognostic imaging biomarkers should provide information of likely disease outcome without treatment, for example the probability of tumour recurrence. However, where the biomarker has been shown to be of prognostic value independent of treatment modality and/or tumour stage (stage often being the main determinant of treatment), a relationship between the biomarker and disease progression without treatment can be inferred.

A range of tumour characteristics of potential prognostic value measured using different imaging modalities have been identified (Table 1). However, none has currently been adopted into routine clinical practice. This article considers key examples of emerging prognostic imaging biomarkers and proposes an evaluation framework that aims to demonstrate clinical efficacy and so support their introduction into the clinical arena.

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Table 1 **Examples of imaging biomarkers with prognostic potential in specific human malignancies**

Imaging technique	Example studies in specific tumours (hazard ratios in parentheses)
[^{18}F]FDG-PET	Head and neck cancer (1.8–2.7)[2–4]
	NSCLC (1.3–10.7)[7–11]]
	Oesophageal cancer (1.0–1.9)[12,14,15,17]
	Colorectal metastases (1.17)[19]
	Lymphoma (1.4–3.1)[23,24]
	Lymphoma, FDG avidity after treatment (7.0–29.7)[20–22]
	Prostate cancer (1.2)[40]
[^{18}F]FLT-PET	Recurrent high-grade glioma (10.1)[30–32]
[^{11}C]Methionine-PET	Brain glioma[33–37]
[^{64}Cu]ATSM-PET	Colorectal primary[18]
$H_2{}^{15}O$-PET	Breast cancer, with dynamic FDG-PET (1.7)[29]
Diffusion-weighted MRI	Glioma[41]
	Prostate cancer (20.8)[42]
	Bladder cancer (6.3)[43]
Dynamic contrast-enhanced MRI	Glioma (7.3)[50]
	Breast cancer (1.0)[51]
Dynamic contrast-enhanced CT	Head and neck cancer[48]
	Colorectal cancer[48]
CTTA	NSCLC (56.0)[44]
	Oesophageal cancer (4.5)[45]
	Liver metastases in colorectal cancer[46]
	Colorectal primary[47]
Doppler ultrasonography	Occult liver metastases[54]
	Melanoma[52]
Dynamic contrast-enhanced ultrasonography	Breast cancer (2.8)[53,55]

Prognostic imaging biomarkers in specific cancers

Positron emission tomography

The glucose analogue [^{18}F]fluorodeoxyglucose (FDG) is by far the most common and important radiotracer in imaging by positron emission tomography (PET). For many malignancies, staging, assessing response to treatment, and monitoring of disease by FDG-PET has become the standard of care. However, to date, there are only limited prospective data for the correlation between tumour metabolism as measured by FDG-PET and improved overall survival.

Head and neck cancer

In several studies of head and neck squamous cell carcinoma (SCC), metabolic tumour volume (MTV) measured by FDG-PET has been shown on multivariate analysis to be an independent prognostic factor for survival[2–5]. Tumour volume expressed as a metabolic index combining MTV and standardized uptake value (SUV) on FDG-PET has also been shown to be valuable for predicting long-term survival in nasopharyngeal carcinoma[6].

Non-small cell lung cancer

MTV has also been studied in patients with non-small cell lung cancer (NSCLC) who subsequently underwent surgical resection of the primary tumour[7]. Preoperative MTV parameters were found to have limited prognostic value for predicting disease-free survival. However, in the same study and several others, multivariate analysis showed that SUV_{max} was an independent predictor of overall survival[7–9]. The European Lung Cancer Working Party also concluded that primary tumour SUV_{max} was of prognostic value for predicting survival in NSCLC[10] in its systematic review and meta-analysis of 1474 patients in 13 studies comparing the hazard ratio for NSCLC patients with a low SUV and those with a high SUV on FDG-PET. A related parameter, the total lesion glycolysis (TLG), which represents the product of MTV and mean SUV, has been shown to predict progression-free survival in NSCLC and has promise as a tool for stratifying patients for risk-adapted therapies[11].

Oesophageal cancer

In a study of oesophageal SCCs by Wieder et al.[12], an association was found between tumour metabolic response and overall survival, whereas Malik et al.[13] concluded that FDG-PET performed during neoadjuvant chemoradiation therapy in oesophageal adenocarcinomas failed to predict survival benefit. A systematic review and meta-analysis conducted by Pan et al.[14] determined that higher SUVs indicated both worse survival prognosis and higher risk of recurrence in patients with oesophageal cancer. Guo et al.[15] also found that SUV and disease

status on PET/CT were significant independent predictors for overall survival in oesophageal SCC, whereas Gillies et al.[16] more recently observed that the very presence of FDG-avid lymph nodes, rather than SUV_{max} or FDG-avid tumour length, correlated negatively with disease-free survival. MTV has been shown to be a better predictor of survival than primary tumour SUV_{max} in patients with oesophageal carcinoma[17].

Colorectal cancer

Dietz et al.[18] reported a pilot study using [^{64}Cu]methylthiosemicarbazone (ATSM) in patients with rectal cancer undergoing neoadjuvant chemoradiotherapy, where higher primary tumour tissue uptake correlated with worse overall and progression-free survival. SUV in colorectal cancer metastases has also been shown to be a significant predictor for overall survival, independent of the subsequent treatment[19].

Lymphoma

In Hodgkin disease and diffuse large B-cell lymphoma, a positive FDG-PET after treatment completion has been shown to be a poor prognostic factor[20–22]. More recently, FDG-PET has also been shown to be an independent outcome predictor in primary central nervous system lymphoma[23]. TLG in FDG-PET was recently found to be a better predictor of survival outcome than the International Prognostic Index for patients with diffuse large B-cell lymphoma[24].

There is early interest in the potential of new PET tracers such as radiolabelled monoclonal antibodies for the management of indolent lymphomas, especially follicular lymphoma, in which the use of FDG-PET/CT is currently not standard practice[25]. However, a positive FDG-PET after induction treatment has been shown to predict a shorter progression-free survival in several studies of patients with follicular lymphoma[26,27].

Melanoma

Melanoma typically demonstrates avid uptake of FDG, making FDG-PET an excellent tool for the detection of primary and metastatic melanoma and quantification of FDG uptake by SUV. In a multivariate analysis of 80 patients with melanoma, mean tumour SUV, along with the number of positive nodes, extranodal growth and gender, were each shown to be independently associated with disease-free survival[28].

Breast cancer

PET tumour blood flow assessment using $H_2{}^{15}O$ combined with dynamic [^{18}F]FDG-PET evaluation (where FDG metabolic and transport rates were quantified) allowed prediction of survival outcome in patients with locally advanced breast cancer in a study published by Dunnwald et al.[29].

Brain glioma

FDG-PET has limited value in the assessment of brain malignancies due to the high intrinsic background uptake and utilization of glucose by the brain. [^{18}F]Fluorothymidine (FLT) has been shown to predict survival in patients with recurrent high-grade glioma[30–32]. [^{11}C]Methionine uptake has been correlated with histologic grade in gliomas, and several studies have also found it to be a useful prognostic imaging biomarker for predicting survival in patients with glioma[33–37], whereas its prognostic value has not been demonstrated in other studies[38,39].

Skeletal scintigraphy

Recently, the Bone Scan Index, which has been developed as a quantitative tool for expressing the tumour burden in the bone as a percentage of total skeletal mass, has been shown to be associated with survival in patients with prostate cancer[40]. The authors of this study demonstrated that quantifying the extent of skeletal metastatic disease on ^{99m}Tc bone scan at the time of diagnosis can be of value in patient management when deciding on treatment.

MR diffusion imaging

Diffusion-weighted MRI produces information about tissue cellularity and the integrity of cellular membranes by probing the movement of water molecules in biological tissues. Tissue characterization is made possible by comparing differences in the apparent diffusion between tissues (e.g. free water movement within a neoplasm would be more restricted than in a simple cyst).

A recent meta-analysis of survival data in malignant astrocytomas has also demonstrated that survival rates in high-grade (3 and 4) tumours had a significant correlation with apparent diffusion coefficient (ADC) values, independent of tumour grade[41], suggesting an important prognostic role in the imaging of gliomas. In prostate cancer, multivariate analysis showed that tumour ADC predicted the likelihood of biochemical recurrence in prostate cancer better than all other variables (including Gleason score, serum prostate-specific antigen and tumour volume)[42]. Similarly, in patients with superficial bladder cancer, pretreatment ADC values at MRI have been shown to be a significant independent predictor of tumour recurrence after transurethral resection[43].

CT texture analysis

Texture analysis involves postprocessing of CT data using software that quantifies disuniformity of tumours at a range of spatial scales. CT texture analysis (CTTA) has shown promise as an independent predictor of survival in patients with advanced NSCLC and oesophageal cancer and could contribute to disease risk stratification for these patients[44,45]. In colorectal cancer, Miles et al.[46]

reported that CTTA of the liver was a better predictor of survival postoperatively than CT perfusion. Recent data from a study conducted by Ng et al.[47] found that contrast-enhanced CTTA of whole primary tumour can predict 5-year overall survival in patients with colorectal cancer.

Perfusion imaging

CT and MR perfusion using iodinated contrast and gadolinium, respectively, provide the ability to non-invasively quantify microvascular blood flow of tissue. Perfusion imaging has given rise to several important quantitative parameters chief among which are blood flow (BF), blood volume (BV), time to peak flow, capillary permeability and the related concept of permeability surface area product (PS), which may have prognostic usefulness in assessing neoplasms.

Bisdas et al.[48] found that high BF and PS on CT perfusion were not only predictive of longer tumour control than patients with hypoperfused upper aerodigestive tract SCC, but that BF-BV mismatch also predicted longer overall survival after chemoradiation. Koh et al.[49] also recently published promising results for the use of kinetic modelling of dynamic contrast-enhanced CT data to predict 5-year overall survival in patients with primary colorectal cancer.

Tumour microvascular permeability and contrast enhancement on MR perfusion imaging have been shown to predict worse short-term (2 years) progression-free survival in low-grade gliomas[50]. In patients with breast cancer, dynamic contrast-enhanced MR parameters, such as maximal tumour enhancement within the first minute of contrast injection and maximal rate of enhancement, have been observed to be superior to traditional prognostic parameters (such as tumour size and nodal metastasis) in the prediction of disease-free and overall survival[51].

Doppler ultrasonography

Tumour angiogenesis evaluated with Doppler sonography has been used to identify early breast cancers and melanomas with higher metastatic potential[52,53]. Neoangiogenesis was additionally found to be an independent predictor of overall survival in early breast cancer[52].

Leen et al.[54] successfully used the Doppler perfusion index (DPI), defined as the ratio of hepatic arterial to total liver BF, to detect subtle changes in hepatic haemodynamics indicating the possibility of occult liver metastases from colorectal cancer in patients who have had apparently curative surgery. The authors found that DPI was a better prognostic factor for predicting early death (within 2 years of diagnosis) than the recognized gold standard of Dukes pathologic classification.

Contrast-enhanced ultrasonography

Microbubble contrast agents administered intravenously into the systemic circulation allow the bloodstream's echo to be enhanced on ultrasonographic imaging, thus allowing blood to be distinguished from surrounding tissues and the evaluation of tumour vascularity and angiogenic activity. Intratumoural BF measured by vessel positive total area on contrast-enhanced ultrasonography has been shown to inversely correlate with overall and tumour-free survival in patients with node-negative breast cancer[55].

Evaluative framework for prognostic imaging biomarkers

The clinical adoption of diagnostic applications of imaging is supported by an established framework that comprises a hierarchical evaluation of evidence that sequentially assesses technical performance, diagnostic performance, diagnostic impact, therapeutic impact and health impact[56]. Although a system for the qualification of imaging biomarkers in oncologic drug development has been proposed[57], there is currently no equivalent framework for the evaluation of imaging biomarkers for clinical use. However, the approach used by MacKenzie and Dixon[56] for diagnostic applications of MRI can be adapted for prognostic imaging biomarkers, correspondingly considering biological/technical performance, prognostic performance, prognostic impact, therapeutic impact and health impact (Fig. 1).

Biological/technical performance

Without a clear biological correlate, interpretation of imaging biomarkers can be problematic. Biological correlates for imaging biomarkers are frequently identified as a result of correlative studies against a range of pathologic features. When the pathologic feature is known to be of prognostic significance, this correlative approach can accelerate imaging biomarker development[58]. Many pathologically based biomarkers reflect expression of particular genes or molecules, whereas imaging biomarkers typically reflect phenotypic characteristics. Therefore, direct one-to-one correlation between pathologic and imaging biomarkers is unlikely and imaging biomarkers may have several pathologic correlates, each of which has some relationship to the phenotypic feature measured by imaging. Table 2 summarizes likely biological correlates for the imaging biomarkers described above.

The technical performance refers to how well an imaging biomarker measurement made in one patient compares with measurements made on another occasion or on a different device in another institution. These sources of variability can be quantified as intra- and interobserver variation. Measurement consistency is increased by the adoption of standardized image acquisition and

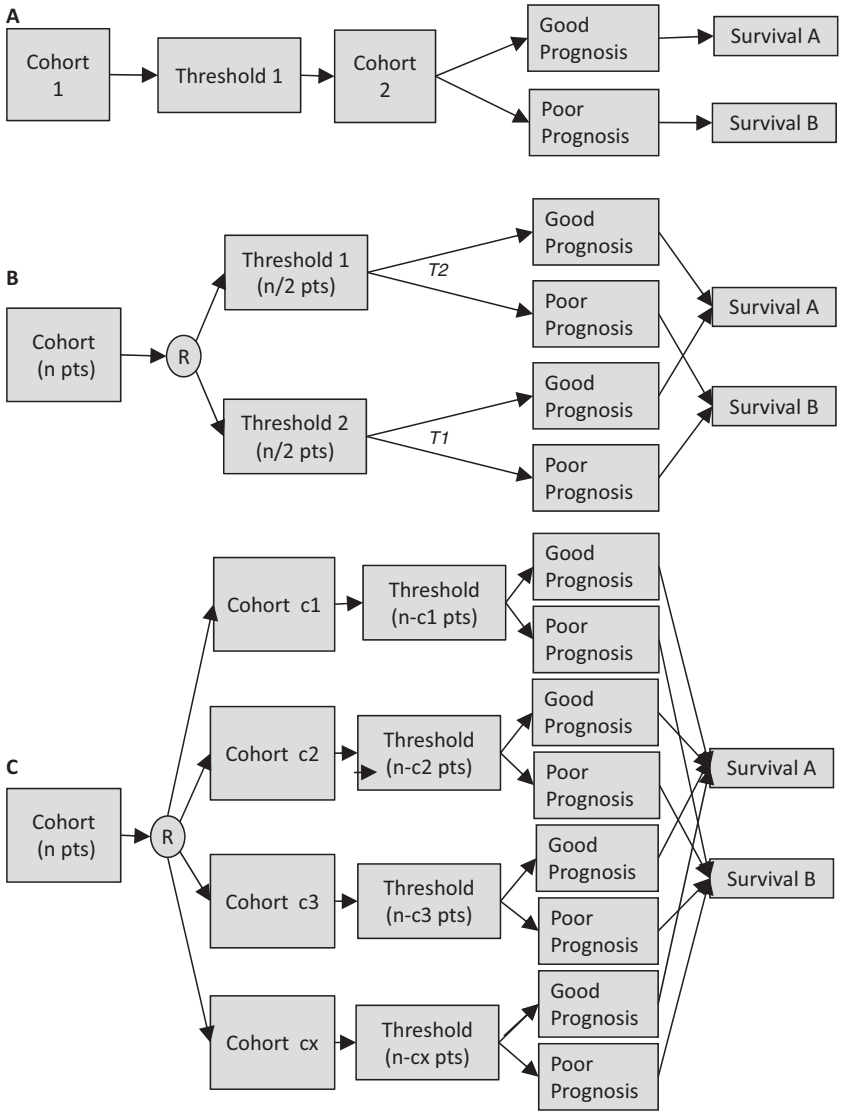

Figure 1 **Methods for obtaining unbiased estimates of prognostic imaging biomarker thresholds. (A) Separate cohorts; (B) two-sample cross-validation; (C) leave-one-out cross-validation.**

Table 2 **Biological correlates for a range of prognostic imaging biomarkers**

Imaging biomarker	Pathologic correlate
FDG-PET	GLUT-1 and hexokinase expression
Skeletal scintigraphy	Osteoblastic activity
Diffusion-weighted MR	Cellularity, necrosis, cell membrane integrity and inflammation[59]
CTTA	Hypoxia and angiogenesis[60]
Perfusion imaging (CT, MR, ultrasonography): tumour	Microvascular density and vascular endothelial growth factor[61–63]
Perfusion imaging: Liver	Micrometastases[64]

processing procedures. Recommended procedures have been published for a range of imaging biomarkers[61,65,66].

Prognostic performance

The imaging community is familiar with parameters for evaluation of diagnostic performance such as sensitivity and specificity. The equivalent parameters that encapsulate prognostic performance are hazard ratio and biomarker prevalence. Hazard ratio reflects the risk of mortality or recurrence in patients identified by the biomarker to have a poor prognosis relative to patients classified as having a good prognosis. The biomarker prevalence indicates the proportions of patients defined by the

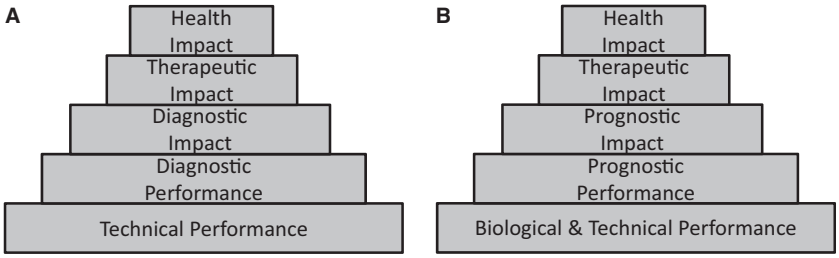

Figure 2 **Evaluation frameworks for diagnostic (A) and prognostic (B) applications of imaging in clinical practice.**

biomarker as having a good or poor prognosis. Multivariate analysis is required to demonstrate that the prognostic performance of the biomarker is independent of other known factors associated with survival such as age, tumour stage, and other imaging biomarkers.

Prognostic imaging biomarkers entail a defined threshold value against which measurements obtained in individual patients are compared. Values falling above or below the threshold determine whether the patient is classified as having a poor or good prognosis. Many studies reporting an association between a quantifiable imaging characteristic and prognosis have established this threshold in a single cohort of patients and then used this threshold to determine prognostic performance in the same cohort. This approach results in a biased overestimation of prognostic performance. A range of cross-validation approaches can be used to avoid this bias, as summarized in Fig. 2. The most straightforward approach is to establish the threshold value in one cohort and apply this threshold to a separate cohort (Fig. 2A). A cross-validation approach (Fig. 2B) randomly divides a cohort into two, usually matched to ensure similar rates for mortality or recurrence. The threshold value established in one cohort is then used to classify patients in the other cohort and vice versa. The resulting poor and good prognosis groups are then combined to calculate the hazard ratio and biomarker prevalence. A leave-one-out approach (Fig. 2C) divides a single cohort into several groups (or even individual patients). Patients in the left-out group are classified based on a threshold established from the remaining groups combined. The process is repeated until all patients have been classified. Good and poor prognosis groups are then combined to determine overall prognostic performance.

Prognostic impact

Prognostic impact refers to the change in prognosis that results from deployment of the imaging biomarker. The potential prognostic impact of imaging biomarkers can be demonstrated using currently available clinical decision tools that allow for incorporation of prognostic biomarkers. An example decision tool is Adjuvant! Online, which aims to assist with decisions concerning adjuvant chemotherapy for lung, colon and breast cancer by estimating the cancer-related mortality without systemic adjuvant therapy, the reduction in mortality afforded by therapy, and the risks of side effects of the therapy[67]. The hazard ratio and biomarker prevalence values for a prognostic imaging biomarker can be entered into the decision software for a range of clinical scenarios, as recently demonstrated for CTTA[68]. For example, Adjuvant! Online indicates that the 5-year survival rates for a 60-year-old male patient with at T2N0M0 NSCLC and average comorbidities with and without platinum-based chemotherapy would be 58.4% and 64.2%, respectively. Table 3 shows the impact on prognostic estimates resulting from use of an imaging biomarker with a hazard ratio of 2.00 and biomarker prevalence of 50%. The 5-year survival rates with or without chemotherapy have both increased in the good prognostic group but the increase in survival gained by chemotherapy has fallen. On the other hand, the patients with a poor prognosis show decreases in 5-year survival but an increase in the benefit gained from chemotherapy compared with that predicted for patients without biomarker stratification.

Therapeutic impact

Therapeutic impact refers to the ability of a health technology to change the clinical management of patients. Of the publications proposing prognostic imaging biomarkers to date, few have clearly identified clinical situations in which deployment of the biomarker could potentially result in change in therapy. This lack of identifiable potential clinical applications represents a barrier to imaging biomarker development.

A therapeutic impact may exist when the change in prognostic confidence is sufficient to change management. Considering the illustration above for a patient with NSCLC, a previous study reported that most oncologists believe at least a 5% increase in 5-year survival is required to justify platinum-based adjuvant chemotherapy for this tumour[69]. The predicted improvement in 5-year survival of 4.2% for the patients with good prognosis may therefore not be considered sufficient to warrant chemotherapy, suggesting a change in management from that indicated by the 5.8% improvement in survival for patients before stratification with the imaging biomarker.

The potential therapeutic impact can be further quantified by plotting the pretest improvement in 5-year

Table 3 **Illustrative prognostic impact of an imaging biomarker with a hazard ratio of 2 and biomarker prevalence of 50% on the projected 5-year survival rates with and without chemotherapy for a 60-year-old man with NSCLC and average comorbidities (derived using Adjuvant! Online[67])**

	All patients (%)	Good prognostic group (%)	Poor prognostic group (%)
5-year survival without chemotherapy	58.4	67.7	49.1
5-year survival with chemotherapy	64.2	72.1	56.0
Survival benefit from chemotherapy	5.8	4.4	6.9

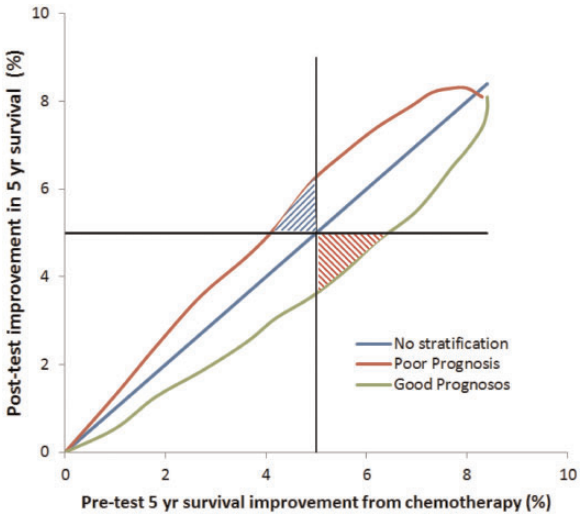

Figure 3 **Estimating the potential therapeutic impact of an imaging biomarker with hazard ratio of 2 and 50% prevalence. The hatched areas represent patients for whom therapy might be altered by the imaging biomarker assuming a 5% improvement in 5-year survival warrants treatment.**

survival from chemotherapy against the post-test improvement in 5-year survival (Fig. 3). Assuming an improvement of 5% justifies chemotherapy, the red-shaded region represents patients with a good prognosis similar to that illustrated above for whom stratification moves the anticipated 5-year survival benefit from treatment to less than 5%. The blue-shaded region represents patients whose prognosis would not have been considered sufficiently poor to warrant chemotherapy before stratification but might be considered to benefit after stratification. The combined area of the shaded regions indicates the ability of the biomarker to affect therapeutic decisions.

Health impact

Health impact refers to improvements in ultimate health outcomes, most commonly survival, that would result from deployment of the imaging biomarker. These health effects can then be compared with the cost implications of biomarker deployment to assess cost-effectiveness. One approach to demonstrating health impact comprises a randomized trial in which health outcomes are compared between two patient cohorts, with the imaging biomarker deployed in one cohort. However, it can be anticipated that the same difficulties recognized to arise from application of this approach to diagnostic uses of imaging will apply equally to prognostic applications[70]. Specifically, the outcomes are primarily determined by the treatment rather than imaging, and statistical variability in the treatment effect tends to mask the effects of imaging such that trials to demonstrate the impact of imaging need to be large, expensive and prolonged. Because of these difficulties, an alternative approach for diagnostic applications has comprised a robust assessment of diagnostic performance followed by decision modelling to assess health impact[70]. A similar approach can be used to demonstrate the health impact of prognostic imaging biomarkers as has been undertaken for the use of CTTA for modifying postoperative surveillance strategies in colorectal cancer[71]. The prognostic performance characteristics required for modelling are the hazard ratio and biomarker prevalence. Modelling also allows these parameters to be varied between their 95% confidence limits to allow for uncertainties in the prognostic performance characteristics.

Future directions

Collaboration

Collaboration among the broad group of stakeholders across health care (public and private clinical providers, government, enterprises in the biopharmaceutical and software vendor industries, researchers and academics) is vital if prognostic imaging biomarkers are to become an integral part of medical practice. The Quantitative Imaging Biomarkers Alliance (QIBA) initiative of the Radiological Society of North America (RSNA) can play an important role in uniting stakeholders in the advancement of quantitative imaging and the use of imaging biomarkers in clinical practice. The establishment of QIBA highlights the increasing importance of quantitative imaging but radiological training is yet to include quantitative imaging on an equal footing with traditional qualitative approaches.

Standardization and multicentre trials

To date, studies investigating the use of imaging biomarkers in survival prediction have mostly been single-centre

studies with relatively small sample sizes, and often differences in chemoradiotherapy regimen, PET acquisition protocols and image analysis. Adherence to standardized recommendations, of which several exist[47,48], will hopefully address many of these issues and increase the opportunity for collaborative research across multiple centres. QIBA undertakes important work in this area but is yet to consider many imaging biomarkers that have progressed furthest through the evaluation framework proposed in this article, for example perfusion CT and CTTA.

Research design and reporting

Prognostic imaging biomarkers have a number of potential advantages over histological assays. Imaging is non-invasive and can assess multiple tumour sites, which is an important consideration given the known heterogeneity of expression of many histological markers. By reflecting the tumour phenotype, imaging biomarkers may potentially be more closely related to tumour behaviour than genetic markers. Approaches in which gene expression and imaging of phenotypic tumour behaviour are assessed collaboratively can be envisaged. However, imaging biomarker research needs to parallel the research designs used in tissue biomarker development. For example, study design should include cross-validation of imaging biomarker thresholds and final reports should state the hazard ratio and biomarker prevalence with 95% confidence intervals to allow subsequent modelling of health and economic impacts.

Conclusion

With appropriate validation within an established evaluation framework, prognostic imaging biomarkers have the potential to contribute to individualized cancer care, in some cases reducing the financial burden of expensive cancer treatments by facilitating their more rational use.

Conflict of interest

K.A. Miles is a director and shareholder of TexRAD Ltd, a supplier of texture analysis software for medical images.

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