The need for molecular predictive signatures in radiation oncology

Recent advances in technological aspects of radiotherapy have paved the way for personalised treatment as they enable the tailoring of radiation doses to individual patients. However, the current optimisation process is primarily focused on dose conformity without taking into account biological factors and it assumes uniform tumour responses to radiation [1].

In medical oncology, genomic signatures have been incorporated into routine practice with tests such as MammaPrint, Oncotype DX, or PAM50. However, the use of such signatures in radiotherapy has been limited. Until now, there has been scarce information available regarding molecular predictive signatures in the field. For instance, the postoperative radiation therapy outcomes score (PORTOS) consists of 24 genes and is used to forecast the effectiveness of postoperative radiotherapy in prostate cancer [2]. Additionally, there are two other classifiers, which are known as the adjuvant radiotherapy intensification classifier (ARTIC) and the profile for the omission of local adjuvant radiotherapy (POLAR). These incorporate 27 and 16 genes respectively. These classifiers have been developed to predict outcomes of the use of postoperative radiotherapy in breast cancer [3,4].

In contrast to cancer-specific indicators such as these, an alternative measure known as the radiosensitivity index (RSI) has been proposed as a universal marker of cellular radiosensitivity that can be applied across various types of cancer [5]. The RSI is calculated based on the expression levels of ten specific genes (*AR, c-JUN, STAT1, PKC, Rel A, cABL, SUMO1, CDK1, HDAC1* and *IRF1*), which are associated with DNA damage-response mechanisms such as cell-cycle regulation, apoptosis induction and proliferation modulation [5]. To enhance its practical applicability in clinical settings for radiotherapy planning purposes, the genomic-adjusted radiation dose (GARD) concept has been developed through the use of RSI values [6].

As an initial validation step, GARD was evaluated in patient cohorts that had been diagnosed with breast, lung and pancreatic cancer, and glioblastoma [6]. Subsequent studies were conducted on a pooled, retrospective sample that encompassed multiple tumour variations. These studies produced new evidence that demonstrated comprehensively that GARD exhibited a strong correlation with key oncological outcomes, such as time until first recurrence and overall survival rates [7]. In another recent study, the use of GARD was explored to explain the outcomes observed in the Radiation Therapy Oncology Group (RTOG) 0617 trial [8]. This model was designed to determine an optimal radiation dose for each patient. In other research that utilised prospectively collected tissue, a correlation was found between low RSI values (which indicate higher radiosensitivity) and increased immune infiltration and activation [9]. Furthermore, a reanalysis of publicly available datasets demonstrated that RSI was associated with immune-related characteristics and could be used to predict responses to blockade therapy that was targeted at the programmed cell-death protein 1 (PD-1) [10-12]. In contrast, another analysis suggested that the application of RSI did not impact survival rates and should not be used to adjust radiation doses [13]. Instead, it has been proposed that evaluation of the tumour clones that remain after radiotherapy may provide better predictions regarding treatment outcomes [14].

Recent studies have furthered the integration of genomic signatures into radiotherapy decision-making (see Table 1). The European Organisation for Research and Treatment of Cancer has recognised the importance of RSI/GARD studies and has prioritised them for phase III clinical trials in radiotherapy [15]. A notable example of such an approach is the ongoing GARD-based trial, the aim of which is to optimise radiotherapy for triple-negative breast cancer (NCT05528133). Further evaluation is necessary to assess the clinical utility of these approaches by integrating molecular data into prospective clinical trials and routine practice.

Table 1. Summary of clinical studies that have investigated the use of radiosensitivity-predicting genomic signatures (adapted from [16], with permission). Key: 95%CI – 95% confidence interval, HR – hazard ratio, sHR – sub-distribution hazard ratio.

Study	Cancer type	Sample size	Main findings
Zhao et al., 2016 [2]	Prostate cancer	526 patients (196 and 330 in training and validation cohorts, respectively)	24-gene predictor of response to postoperative radiotherapy. High

			PORTOS score predicts a lower incidence of distant metastases in both training (HR 0.12, 95% CI 0.03-0.41, p<0.0001) and validation (HR 0.15, 95% CI 0.04-0.60, p=0.002) cohorts.
Tang et al., 2017 [17]	Sarcomas	253 patients from The Cancer Genome Atlas (TCGA)	26-gene radiosensitivity signature. Predicted radiosensitive patients had better overall survival than predicted non-radiosensitive patients (HR 0.07, p<0.001).
Cui et al., 2018 [18]	Breast cancer	948 and 1439 patients in training and validation cohorts, respectively (Molecular Taxonomy of Breast Cancer International Consortium)	34-gene radiosensitivity signature. Patients administered radiotherapy had better disease-specific survival than did those who did not in the radiation-sensitive group (HR 0.68, p=0.059); a reverse effect was observed in the radiation-resistant group (HR 1.53, p=0.059). 4-gene immune signature predictive of radiotherapy benefit. Patients who were administered radiotherapy had significantly better disease-specific survival in the immune-effective group (HR 0.46, p=0.0076), with no difference in disease-specific survival in the immune-defective group (HR 1.27, p=0.16).
Sjöström et al., 2019 [3]	Breast cancer	748 patients from the Swedish breast cancer	ARTIC comprised 27 genes and patient age was prognostic for

		group 91 radiotherapy (SweBCG91-RT) trial	locoregional recurrence in breast cancer patients who were administered radiotherapy (HR 3.4, 95% CI 2.0-5.9, p<0.001) and was predictive of radiotherapy benefit (p=0.005). Patients with low ARTIC scores had a greater benefit from radiotherapy (HR 0.33, 95% CI 0.21-0.52, p<0.001) than those with high ARTIC scores (HR 0.73, 95% CI 0.44-1.2, p=0.23).
Kim et al., 2020 [19]	Head and neck squamous cell carcinomas that were negative for human papillomavirus	203 patients from TCGA cohort	Use of 41-gene radiosensitivity signature predicted reduced five-year recurrence-free survival in the radioresistant group versus the radiosensitive group (57.8% vs. 80.1%; p=0.035)
Scott et al., 2021 [20]	Various types (breast, head and neck, non-small-cell lung, pancreatic and endometrial cancers, melanoma and glioma)	1615 patients, of whom 1298 (982 and 316 with and without radiotherapy, respectively) were assessed for time to first recurrence and 677 (424 and 253 with and without radiotherapy, respectively) for overall survival	GARD was associated with time to first recurrence (HR 0.98, 95% CI 0.97-0.99, p=0.0017) and overall survival (HR 0.97, 95% CI 0.95-0.99, p=0.0007). The effect on overall survival was dependent on radiotherapy use (p=0.011).
Feng et al., 2021 [21]	Prostate cancer	486 of 760 patients randomised in NRG Oncology/RTOG 9601 trial	22-gene genomic classifier (Decipher Biosciences Inc) was associated with distant metastases (HR 1.17, 95% CI 1.05-1.32, p=0.006), prostate cancer-specific mortality (HR 1.39, 95% CI 1.20-1.63, p<0.001) and overall survival (HR

			1.17, 95% CI 1.06-1.29, p=0.002).
Dal Pra et al., 2022 [22]	Prostate cancer	226 of 350 patients randomised in the Swiss Group for Clinical Cancer Research (SAKK) 09/10 trial	22-gene genomic classifier (Decipher Biosciences Inc) was associated with biochemical progression (HR 2.26, 95% CI 1.42-3.60, p<0.001), clinical progression (HR 2.29, 95% CI 1.32-3.98, p=0.003) and use of hormone therapy (sHR 2.99, 95% CI 1.55-5.76, p=0.001). Patients with high and low classifier scores had 45% and 71% five-year freedom from biochemical progression, respectively.
Wu et al., 2022 [23]	Gliomas	1395 from Chinese Glioma Genome Atlas and TCGA	12-gene radiosensitivity predictive index had better predictive capacity than the traditional World Health Organization classification system (concordance index: 0.842 vs. 0.787, $p \leq 2.2 \times 10^{-16}$).
Sjöström et al., 2023 [4]	Breast cancer	729 patients from the SweBCG91-RT trial and Princess Margaret Hospital	16-gene POLAR signature used. POLAR low-risk patients did not benefit from the use of adjuvant radiotherapy (HR 1.1, 95% CI 0.39-3.40, p=0.81; HR 1.5, 95% CI 0.14-16, p=0.74). POLAR high-risk patients had a significantly lower risk of locoregional recurrence when radiotherapy was applied (HR 0.43, 95% CI 0.24-0.78, p=0.006;

			HR 0.25, 95% CI 0.07-0.92, p=0.038).
Spratt et al., 2023 [24]	Prostate cancer	215 patients from NRG Oncology/RTOG 0126	22-gene genomic classifier (Decipher Biosciences Inc) was independently prognostic for disease progression (sHR 1.12, 95% CI 1.00-1.26, p=0.04), biochemical failure (sHR 1.22, 95% CI 1.10-1.37, p<0.001), distant metastasis (sHR 1.28, 95% CI 1.06-1.55, p=0.01), and prostate cancer-specific mortality (sHR 1.45, 95% CI 1.20-1.76, p<0.001).

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