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ADVANCES IN RADIOTHERAPY SPECIAL FEATURE: COMMENTARY

Tailoring cancer radiotherapy through genotyping, how close are we?

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Ever since the discovery of genetic aberration and its fundamental role in cancer induction and evolution, it was clear that the primary way to comprehend and eradicate this disease is through deciphering the molecular code. The huge endeavour of the human international gene project and the consequent exponential advance in high-throughput genetic analysis boosted our understanding of the tumour heterogeneity and the limitations of the current classic clinicopathological classification in predicting treatment outcomes. Under this conviction, cancer research was directed to discover new molecular markers and pathways that can be used in tumour subtyping or targeting; thus aiming to optimize treatment decisions.

The gene analysis technology evolved from a single-gene detection to full genome sequencing, offering genotyping of most cancer types at an affordable cost and reasonable time, which resulted in rapidly accumulating evidence on how to optimize cancer management, both in the primary and the metastatic setting.¹

This considerable basic research effort pushed the genotyping closer to the bedside; Alizadeh et al² demonstrated the value of genetic profiling of diffuse large B-cell lymphoma into two distinct groups with different clinical outcomes. The clinical value of genotyping was equally evident in breast cancer where molecular signature predicts overall survival³ and guides systemic therapy.⁴ Currently, the choice of systemic therapy in lung cancer is guided by the presence of certain molecular markers such as anaplastic lymphoma kinase fusion oncogene⁵ or epidermal growth factor receptor mutation.⁶

Although the majority of the upcoming studies focus primarily on distant failure prediction and on systemic therapy choice, the interplay between systemic and local therapies is becoming important; molecular markers may predict failure patterns pointing to the relative importance of each modality and directing the best timing to incorporate each.

Analogous to systemic therapy, can we use molecular markers to direct radiotherapy choice or select the appropriate dose? Awaiting further evidence, genotyping-based radiotherapy consideration is still evolving, and current research is focusing on molecular signatures to predict locoregional failure and to guide radiation therapy decision-making. For example, Cheng et al⁷ reported on a genomic model predicting post-mastectomy locoregional recurrence with an overall accuracy of 75–78%. They demonstrated that a 34-gene prediction assay can be used to select patients after mastectomy who might benefit from adjuvant radiotherapy, while sparing patients of radiotherapy side effects if their predicted recurrence risk is low. Tramm et al⁸ updated the Danish post-mastectomy experience using seven genes to identify patients whose predicted higher locoregional failure can be reduced with adjuvant radiotherapy. In another study, patients after lumpectomy with a favourable molecular profile experienced 5% local recurrence rate at 10 years compared with 29% in patients with an unfavourable profile. Based primarily on a molecular wound gene signature, this classifier achieved 87.5% sensitivity in predicting local recurrence risk and segregating patients into their corresponding profile.⁹ Another study employed the 21-gene-based OncotypeTM DX (Genomic Health, Redwood City, CA) recurrence score, currently used routinely in the clinical setting to estimate distant recurrence risk and the need for chemotherapy, to predict local recurrence in patients with oestrogen receptor-positive, node-negative breast cancer.¹⁰ In a retrospective analysis of patients treated in the National Surgical Adjuvant Breast and Bowel Project studies, Mamounas et al¹⁰ reported that higher scores predicted higher local-regional recurrence rates in selected patients, thus possibly expanding the use of the 21-gene signature in guiding radiotherapy recommendations in oestrogen receptor-positive patients. Recently, a modification of the Oncotype profile in ductal carcinoma *in situ*, *OncotypeDCIS*,

score was shown to predict local recurrence after lumpectomy alone for breast ductal carcinoma *in situ*.¹¹ After validation of the study findings, this readily available technology may help select patients, with high recurrence score, who may benefit the most from adjuvant radiotherapy. All of these studies present promising data that genetic profiling may help to identify patients most likely to benefit from radiation but larger data sets and validation studies are required to confirm their clinical utility.

The potential clinical benefit from molecular profiling is evident in that we may be able to defer radiotherapy in tumours whose genetic profile predicts excellent outcome with surgery alone, whereas, those whose molecular signature predicts high recurrence rates with radiation alone can be selected for an aggressive approach with either escalated doses of radiation, combination chemoradiotherapy, or targeted therapies to neutralize radioresistant pathways.

Another area that has not been extensively explored is molecular predictors of immune response and stromal response to radiation, which may be targeted to improve outcomes and reduce toxicity in patients undergoing radiation. There is an expanding body of literature that illustrates the effect of stromal and/or immune responses to systemic therapy on tumour control. Yet, molecular predictors of immune and stromal response to radiation is still another area that needs further exploration to tailor radiotherapy based on the patients' unique profile; targeting radioresistant pathways to improve outcomes and circumventing radiosensitive pathways to reduce toxicity. Moreover, novel therapies modulating these molecular pathways may potentially enhance the effectiveness of radiation.

From a technical perspective, the advances in molecular and functional imaging such as positron emission tomography (e.g. mapping hypoxia markers within the tumours) or MR spectroscopy (analysing the spatial distribution of potential radio-resistant cancer cells) may improve our understanding of the various biological phenomena related to cancer biology. In addition to guiding clinical decision-making, these imaging techniques may allow a more precise radiotherapy planning process through multimodality image-guided radiotherapy; thus enhancing the therapeutic ratio. These molecular-driven imaging approaches can allow early localization of recurrent disease while, at the same time, help to guide radiation therapy delivery.

Although the genomic research is advancing at a fast rate, widespread clinical use is hindered by several logistic and economic challenges. Continuous support of basic research coupled with multi-institution validation of these studies using a unified platform is required to streamline the technology into the clinic. Innovative clinical study design accounting for time and economical adversities combined with organizational collaboration to share data is needed to mitigate the limitation of the present study design and speed up the process.

Stepping into the genomic era marks a point in cancer management history; for the first time, the current molecular techniques, accompanied by all our past knowledge, can provide a tool directly applicable in clinics. Despite the challenges, this decade will undoubtedly witness significant breakthroughs in cancer management, improving outcomes and quality of life, and hopefully getting closer to our goal to eradicate the disease.

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