Radiosensitivity index as a predictive biomarker for radiotherapy de-intensification in nasopharyngeal carcinoma: abridged secondary publication

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KEY MESSAGES

1. The radiosensitivity index is a potential predictor for locoregional control in radiotherapy-treated patients with locally advanced nasopharyngeal cancer.
2. Owing to the small sample size, the association between radiosensitivity index and late toxicity is inconclusive.

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Introduction

In 2018, nasopharyngeal carcinoma (NPC) affected more than 70 000 individuals worldwide. Radiotherapy (RT) is the primary treatment for NPC; patients with the same tumour, node, and metastasis stage receive similar doses of RT based on a stage-based strategy.[1]

Improvements in anatomic precision can increase tumour control and decrease complications. Intensity-modulated RT improves the 5-year locoregional control rate to approximately 90%, even in patients with locally advanced NPC. However, treatment for NPC continues to use the stage-based strategy, whereby tumours with similar anatomic extent receive identical doses of radiation. This one-size-fits-all approach fails to address the biological heterogeneity of cancer.

Moffitt Cancer Center has developed a gene expression-based radiosensitivity index (RSI),[1] which was validated as an independent predictor for clinical outcomes in RT-treated patients. The genomic-guided radiation dose model integrates the gene expression-based RSI with a linear quadratic model of radiation prescription to establish a precision medicine framework for radiation oncology.[2] Personalised RT for patients with NPC also addresses tissue-related complications. The Radiogenomics Consortium considers radiation toxicity to be genetically predetermined. The radiosensitivity pathway in NPC is used to predict tumour control and late toxicity incidence.[3] We hypothesised that the RSI can serve as a predictive biomarker for tumour control, survival, and late toxicity. We aimed to evaluate the predictive value of the RSI in RT-treated patients with locally advanced NPC.[4]

Methods

We analysed archived specimens from the NPC-0501 trial.[4] In total, 803 patients with locally advanced NPC (stage III to IVb) were recruited between September 2006 and September 2012. Pre-treatment formalin-fixed, paraffin-embedded tissue samples were available from 243 patients; 71 samples were excluded owing to inadequate tumour cells. Therefore, 172 samples were reviewed, but 80 of the samples demonstrated poor quality. The remaining 92 samples were analysed using the RSI model.

Results

Of the 92 patients with NPC included, 74 were classified as radiosensitive (RS) and 18 were classified as radioresistant (RR). The two groups were comparable in terms of demographics.

At the median follow-up interval of 7.1 (range, 0.8-11.9) years, 27 patients had died of disease progression (n=26) or brain abscess (n=1). RS patients had higher rates than RR patients in terms of the 3-year and 5-year locoregional failure-free rates (84.4% vs 64.9% and 84.4% vs 51.4%, respectively; P=0.001, adjusted P=0.009) as well as the 3-year and 5-year overall survival rates.

Of the 92 patients, 20 developed severe (≥grade 3) late toxicity: peripheral neuropathy (n=9, 9.8%), ear-related (deafness/otitis) [n=9, 9.8%], and soft tissue/bone damage (n=3, 3.3%). The RS and RR patients were comparable in terms of the incidence of late toxicity (P=0.491) and serious late toxicity-free rate (P=0.532).

Discussion

NPC is radiosensitive; we identified genomically distinct patient populations who experienced differential benefits from radiation. The RSI is an independent predictor for survival outcomes among RT-treated patients with NPC, consistent with reports that the RSI is an assay of radiosensitivity independent of disease sites. Our genomic-guided radiation dose model provides a framework for adjusting RT doses among patients with NPC according to individual tumour radiosensitivity.

The use of a biomarker-based model to guide RT prescription may improve treatment outcomes. The RSI has been biologically and clinically validated. Use of the RSI may avoid multiple tests, and use of a pre-defined cut-off may avoid potential bias. All patients included were participants in a phase III multicentre randomised controlled trial (NPC-0501 study); the tissue specimens were prospectively collected. The clinical validity of the RSI is supported by level I scientific evidence.

The RSI is an independent predictor for locoregional control in RT-treated patients with locally advanced NPC. Patients with primary NPC received uniformly high-dose radiation (66-76 Gy); the dose of RT may have eliminated differences in tumour radiosensitivity; only high RR tumours will develop local recurrence. However, patients harbouring microscopic disease usually receive a modest dose of radiation (50-60 Gy); radiosensitivity becomes relevant because larger numbers of such patients receive insufficient radiation doses.

There was no correlation between the RSI and the incidence of late toxicity, contrary to our hypothesis that radiosensitivity of tumour and normal tissue is related. Candidate gene studies and genome-wide association studies are needed to identify biomarkers that can predict normal tissue toxicity.

The present study had several limitations. The sample size was small. Patients were randomised into six treatment arms, which may have affected clinical outcomes. Data were obtained from an endemic region where the main NPC subtype is undifferentiated non-keratinising carcinoma. All included patients had locally advanced NPC tumours (T3/4 or N0-3) and were treated with concurrent chemotherapy plus (neo)adjuvant chemotherapy.

Conclusion

The RSI is an independent predictor for survival outcomes, but not toxicity, among RT-treated patients with NPC.

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