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Original Research

Survival impact of waiting time for radical radiotherapy in nasopharyngeal carcinoma: A large institution-based cohort study from an endemic area

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Abstract ***Background:*** Whether the waiting time for radical radiotherapy (WRT) detrimentally impacts nasopharyngeal carcinoma (NPC) prognosis is unclear. We estimated the influence of WRT on overall survival (OS) and disease-specific survival (DSS) of NPC.
Patients and methods: Patients were identified from prospectively maintained database. WRT was calculated from histological diagnosis to initiation of radiotherapy (RT). Survival analysis was estimated using Weibull parametric model and propensity score analysis (PSA). Recursive partitioning analysis (RPA) identified optimal WRT threshold via conditional inference trees to estimate the greatest survival differences based on randomly selected training and validation sets, and this process was repeated 1000 times to ensure threshold robustness. Sensitivity

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Recursive partitioning analysis;
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ASARA

analysis estimated effects of potential unmeasured confounders.
Results: A total of 9896 patients were included. In multivariate analysis, WRT of 31–60°d, of 61–90°d and of greater than 90°d independently increased mortality risk compared to less than 30°d. Upon RPA, ranges of 30–35°d with the peak of 30°d were confirmed with 89% of simulations validating optimal thresholds. In threshold-based groups, adjusted hazard ratios (HRs) for WRT of greater than 30°d by both Weibull model and PSA were significantly higher than for WRT of less than 30°d [OS: HR = 1.13, 95% confidence interval (CI) 1.04–1.23, $P = 0.003$; DSS: HR = 1.15, 95% CI 1.05–1.26, $P = 0.002$]. Sensitivity analysis revealed robustness of results.
Conclusions: WRT independently affects survival. Increasing WRT beyond 30°d was most consistently detrimental to survival. WRT of NPC should be as short as reasonably achievable (ASARA).

1. Introduction

The waiting times of definitive cancer treatment in healthcare is a heavily debated subject [1–3]. Generally, oncologists believe that early radical treatment is desirable after cancer diagnosis, and patients hope to receive definitive treatment as early as possible. However, in many cases, timely treatment is hindered by social factors such as low-efficiency healthcare process, limited medical resources, and absence of policy support and by treatment-related factors, such as comorbidities, examinations and auxiliary therapy [3]. Long waiting times can be an indicator of healthcare access and might imply an inability to pay, an imbalance of medical resources and a low-efficiency utilisation and poor-quality medical care [4,5]. Importantly, longer waiting times have been associated with worse prognosis for many tumours originating at assorted primary sites, including breast [6], rectal [4], uterine [2] and bladder tumours [7]. The relationship between longer waiting time and poorer outcomes has been explored in terms of tumour progression [8–10] and psychological pressure [11]. Radiotherapy (RT) is a critical and inseparable part of comprehensive cancer treatment and control. Due to the increasing incidence of tumour, however, the burden of cancer is expected to rise worldwide without a commensurate investment on essential medical resources of RT [3]. Consequently, this unacceptably low level of access to RT causes seriously long waiting time for radical RT (WRT) directly.

Nasopharyngeal carcinoma (NPC) is a specific type of head and neck squamous cell carcinoma (HNSCC) with an aggressive nature and special epidemiological feature [12]. Due to the radiosensitive behaviour of NPC and its deep-seated anatomical location, RT is the cornerstone of its radical treatment technique [12]. Unfortunately, impacts of WRT on the survival of NPC patients have not been clearly demonstrated with large enough cohort of patients. Therefore, whether a threshold does exist beyond which increasing WRT detrimentally impacts NPC prognosis needs further exploration.

In this study, our aim was to estimate the influence of WRT on overall survival (OS) and disease-specific survival (DSS) in a large cohort of NPC patients from an endemic area.

2. Materials and methods

2.1. Patient

This study was approved by the Institutional Review Board of Sun Yat-Sen University Cancer Center (SYSUCC), Guangzhou, China. All NPC patients treated by RT with curative intent from January 1998 to August 2013 were identified from a prospectively created database. Of the primary cohort containing 12,886 NPC patients, 2990 patients were excluded from the analysis. The primary cohort exclusion criteria are detailed in the Supplementary Materials. Finally, a total of 9896 patients were included in this study.

2.2. Treatment and follow-up

All patients were treated according to the principle of treatment for NPC at SYSUCC, and examined every 3°months during the first 3°years and then every 6°months after treatment thereafter until death. Detailed information is presented in the Supplementary Materials.

2.3. Outcome and variable definitions

The primary outcome was OS, which was defined as the interval from the date of histological diagnosis to the date of death. The secondary outcome was DSS, which was calculated from diagnosis to death from tumour. WRT was defined as the interval between the date of diagnosis and the first day of RT. The date of diagnosis