



Suggestions for radiation oncologists to overcome radiotherapy interruption in patients with nasopharyngeal cancer

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In this issue of *Radiotherapy and Oncology*, Yao and colleagues report the results of intensity-modulated radiation therapy (IMRT) interruption in patients with nasopharyngeal carcinoma based on big-data intelligence platform analysis including 7,826 patients (1). They showed that increasing radiotherapy (RT) interruption to 7 or more days was significantly negative for survival. Evidently, tumor repopulation during RT affects treatment results, as well as the famous 4R principle of RT, i.e., repopulation, repair, reoxygenation, and redistribution. From this perspective, the total treatment time was an object of concern. In hindsight, the Radiation Therapy Oncology Group (RTOG) 9003 was one of the largest phase III randomized controlled trials, with more than 1,000 enrolled patients with head and neck squamous cell carcinomas, evaluating altered fractionation schedules against standard fractionation (2). The results showed that altered fractionation with shorter treatment duration was superior to standard fractionation in terms of local tumor control at the expense of acute toxicity, despite having no difference on overall survival.

Tumors grow with the progression of time and, along with 4R, tumor doubling time is an important issue in cancer treatment. Multiple studies showed negative effects of waiting time on patients with head and neck cancer. A recent pilot study by Delahaut *et al.* revealed that treatment delay should be avoided due to the mean absolute tumor progression velocity of 0.23 ± 0.2 cm³/day in 19 patients with

head and neck squamous cell carcinomas (3). One Danish study reported that the tumor volume doubling time, which was normally a median of 99 days, was reduced to 30 days for those with the fastest growing tumors, accounting for half the patient population (4). Majority of these patients developed significant signs of tumor progression within an average of 4 weeks.

Currently three studies are available regarding treatment interruption during IMRT in patients with nasopharyngeal carcinoma (1,5,6). Two research groups, Yao *et al.* and Xu *et al.*, reported significant adverse effects of treatment interruption of ≥ 7 and ≥ 4 or more days on overall survival, respectively (1,5). Yao *et al.* showed a 5-year overall survival of the interrupted *vs.* uninterrupted groups of 82.4% and 86.5%, respectively ($P=0.001$), while Xu *et al.* reported a 3-year overall survival rate of 80.8% and 87.9%, respectively ($P<0.05$). However, one study by Li *et al.* did not find a significant difference in treatment results, including overall survival (6). Nevertheless, considering the numerous reports in support of the evidence, the negative effect of treatment interruption should not be trivialized. Furthermore, practically designing a randomized controlled trial for treatment interruption has challenging ethical considerations. The relationship of radiation treatment time and overall survival was also observed in not only patients with nasopharyngeal cancer but also patients with locally advanced non-small cell lung cancer (7). From the National

Cancer Database, 14,154 patients with stage III non-small cell lung cancer were included in this North American study. The median overall survival rate was significantly worse for the prolonged rather than the standard radiation treatment time (7).

The causes of treatment interruption could be stratified into two categories: delay in treatment initiation and interruption during the treatment. The former was observed in several studies, and the main reason is delayed diagnosis and treatment (3,4,8). While the latter might be more complex and the patient, disease, and treatment factors must be considered (1,7,9,10). Patient factors (age, sex, performance status, and socioeconomic status), disease factors (tumor site, and TNM stage), and treatment factors (RT, surgery, and a combination of chemotherapies) should be considered.

Several approaches have been identified to overcome the detrimental effects of treatment delay or interruption. Here we suggest three such ways.

First, radiation oncologists need to respond flexibly to reduce the adverse effects of treatment delay. Hypofractionation is an efficient way to shorten the overall treatment time with reduced acute toxicity. Shaitelman *et al.* reported the results of a phase III randomized trial comparing conventional fractionated versus hypofractionated whole-breast irradiation in terms of acute and short-term toxic effects in patients with breast cancer (11). The hypofractionated group appeared to yield lower acute toxicities than those of the conventional group in this study. Six days' treatment per week could also be an alternative to counteracting interruptions by treating patients on Saturday to maintain the overall treatment time without loss of local control. Introduction of fractions on public holidays was also suggested to manage interruptions in case of treatment delay in terms of tumor control probability (12).

Second, scrupulous attention is needed for proper supportive care during radiotherapy to avoid excessive acute toxicity of grade three or higher. In the case of patients receiving concomitant RT with cetuximab, more severe forms of radiation dermatitis are expected than that caused by cisplatin-based chemoradiation. Bonomo *et al.* reported that routine advanced wound care from the beginning of the treatment is necessary, and calcium alginate dressings should be considered in case of moist desquamation by reducing the mean radiation treatment interruption from 8.42 days (SD, 6.73; 95% CI, 5.7–11.1) to 0.86 days (SD, 2.66; 95% CI, 0.28–2.02) in patients with concurrent RT combined

with cetuximab (13). A topical steroid could be considered for the prevention of radiation dermatitis after conventional 50–60 Gy irradiation for the patients with breast cancer (14). A recent phase III study is ongoing to show the benefit of topical steroids over placebos for radiation dermatitis induced by definitive chemoradiotherapy with a high dose of over 60–70 Gy in patients with head and neck cancer (14). Similar to dermatitis, a certain extent of oral mucositis is inevitable after RT with curative aim for the head and neck region. Decreased oral intake due to mucositis leads to weight loss and weakness. There is no consensus on nutritional intervention in patients with head and neck cancer undergoing RT with a lack of large prospective studies. However, one small prospective study reported that nutritional intervention for patients with head and neck cancer receiving curative RT to prevent severe weight loss resulted in 90% of patients completing RT without interruption of oral feeding and 17% of patients needing enteral nutrition (15). In addition, enteral feeding with percutaneous endoscopic gastrostomy is one of the assured ways to prevent unexpected treatment interruption during RT (16,17). In particular, prophylactic percutaneous endoscopic gastrostomy before the initiation of RT (16) or no later than the radiation therapy dose of 30 Gy (17) is recommended according to the literature. As a reference, the UK national multidisciplinary guidelines on nutritional management in head and neck cancer was reported and is worthy of note for the daily care of patients under clinical setting (18).

Finally, a good rapport with patients and dedicated cooperation with partners in a multidisciplinary team are key to achieve these goals. Overcoming psychological problems, which are easily overlooked, are an important issue in terms of building good relationships with patients. According to Chen *et al.*, pretreatment depression has a significant correlation with RT treatment interruption and inferior survival in patients with head and neck cancer (19). Continuous RT breaks of more than 5 days occurred in 46% of patients whose mood was “extremely depressed” in self-reported responses to the mood and anxiety domains of the University of Washington Quality of Life instrument, and 23% of them did not complete their planned RT. This result correlated with a statistically inferior 2-year overall survival rate.

Thus, comprehensive care with physical and psychological intervention for patients is key to ensure strict adherence to the scheduled treatment and achieve optimal treatment outcomes.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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