



Clinical Investigation

Final Report of a Prospective Randomized Trial to Evaluate the Dose-Response Relationship for Postoperative Radiation Therapy and Pathologic Risk Groups in Patients With Head and Neck Cancer



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Summary

We present the final report of a phase 3 trial to assess dose response for postoperative

Purpose: To present the long-term and final report of a phase 3 trial designed to assess dose-response relationship for postoperative radiation therapy (PORT) and pathologic risk groups in head and neck cancer.

Methods and Materials: Patients who underwent primary surgery for American Joint Committee on Cancer stage III or IV squamous cell carcinoma of the oral cavity,

Note—An online CME test for this article can be taken at <http://astro.org/MOC>.

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radiation therapy in head and neck cancer. Primary sites and involved necks were independently assigned to higher- or lower-risk categories based on a point score system and then randomized to receive different dose levels. Increasing dose did not significantly improve tumor control, treatment package time was the only significant treatment variable, and positive surgical margins and extracapsular extension were the most significant pathologic factors.

oropharynx, hypopharynx, or larynx and who required PORT were eligible. Patients' primary sites and involved necks were independently assigned to higher- or lower-risk categories based on a cumulative point score representing increasing risk of recurrence. The sites in the lower-risk group were randomized to receive 57.6 or 63 Gy and those in the higher-risk group were randomized to receive 63 or 68.4 Gy, all at 1.8 Gy per fraction.

Results: A total of 264 patients were included. The actuarial 5-year locoregional control rate was 67%. A second primary cancer was documented in 27% of patients. The 5- and 10-year freedom-from-distant metastasis rates were 64% and 60%, respectively, whereas the 5- and 10-year overall survival rates were 32% and 20%, respectively. There was no statistically significant difference in tumor control between different dose levels in both the lower- and higher-risk groups. On multivariate analysis, nonwhite race ($P=.0003$), positive surgical margins ($P=.009$), extracapsular extension (ECE, $P=.01$), and treatment package time (TPT) ≥ 85 days ($P=.002$) were independent correlates of worse locoregional control, whereas age ≥ 57 years ($P<.0001$), positive surgical margins ($P=.01$), ECE ($P=.026$), and TPT ≥ 85 days ($P=.003$) were independently associated with worse overall survival.

Conclusions: This long-term report of PORT delivered at 1.8 Gy/d to total doses of 57.6 to 68.4 Gy without chemotherapy for head and neck squamous cell carcinoma demonstrated that increasing dose did not significantly improve tumor control. On multivariate analysis, the only significant treatment variable was TPT. The results confirm that positive surgical margins and/or nodal ECE remains the most significant predictive pathologic factors. © 2017 Elsevier Inc. All rights reserved.

Introduction

Gilbert Fletcher introduced the concept of postoperative radiation therapy (PORT) for head and neck squamous cell carcinoma (HNSCC) in the 1950s to address observed high rates of postoperative recurrences (1). Subsequent reports confirmed that PORT can improve disease control—and probably survival—but there were no uniform or prospectively validated guidelines for fractional or total radiation dose selection (2-6). Fletcher (7) recommended a radiation dose of 60 Gy in the second edition of his *Textbook of Radiotherapy*. He posited in this era antedating segmental imaging that an incremental dose of 10 Gy was required to overcome relative hypoxia in the operative bed whereas nonoperated, non-tumor-bearing volumes could be reliably controlled with just 50 Gy. The University of Florida recommended that the dose be increased to 65 Gy at 1.7 to 1.8 Gy per fraction and that higher-risk areas, including positive margins, receive a definitive intent dose of 70 Gy (8). Thus, despite recognition of a benefit to PORT, questions regarding the ideal fractional dose and total dose, as well as the need for additional dose if clinical and pathologic features suggested a greater risk of recurrence, remained unanswered. To address these questions, investigators at The University of Texas MD Anderson Cancer Center evaluated the dose-response relationship for head and neck cancer PORT with this prospective, randomized study between 1983 and 1991. The question regarding fractional dose (ie, 1.8 Gy vs 2 Gy) was deemed less important, so these scientists focused on total dose, which varied dependent on a risk stratification formula based on the then-current understanding of clinical, surgical, and pathologic factors.

A preliminary report on the first 240 of 302 patients was published in 1993 with a median follow-up period of 22 months (9). The authors recommended a dose of 57.6 Gy for “intermediate-risk” volumes and 63 Gy for “high-risk” volumes delivered at 1.8 Gy per fraction, 5 days per week. More complete long-term follow-up data were collected but not reported. The authors recognized that treatment time factors were important and, in fact, addressed these in their next trial, randomizing patients to standard or accelerated fractionated PORT.

We analyzed the >20-year follow-up on the original dataset for the complete cohort and performed further unplanned exploratory statistical analyses in light of the current understanding of risk factors to better appreciate the time-dose-response relationships for PORT in HNSCC. Our specific aims include:

1. Long-term and final reporting of this prospective, risk-adaptive trial
2. Confirmation of tumor risk factors affecting outcomes after PORT without chemotherapy
3. Identification of time- and/or dose-dependent outcomes in PORT without chemotherapy
4. Identification of treatment package time (TPT, from surgery to completion of PORT) thresholds for PORT in HNSCC

Methods and Materials

The details of the study design, inclusion criteria, risk stratification, and radiation therapy (RT) techniques were

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