Diagnosis-to-Treatment Interval and Control of Locoregionally Advanced Head and Neck Cancer

Jimmy J. Caudell, MD, PhD; Julie L. Locher, PhD; James A. Bonner, MD

Objective: To assess the impact of prolonged diagnosis-to-treatment interval (DTI) that falls in the time frame associated with the increasing complexity of planning treatment for patients with locoregionally advanced head and neck cancer (LAHNC).

Design: Retrospective study.

Setting: The University of Alabama at Birmingham.

Patients: An institutional database was searched for all patients with LAHNC who were treated with radiotherapy between 1995 and 2007 at the University of Alabama at Birmingham. After patients with prior treatment for head and neck cancer (including surgery or neoadjuvant chemotherapy), patients younger than 18 years, and patients with stage I or II tumors were excluded, 427 patients remained for analysis.

Main Outcome Measures: The DTI was defined as the time in days between the date that a biopsy specimen showing malignancy was obtained and the first day of radiotherapy.

Results: The median DTI was 34 days (range, 7-441 days). A longer DTI was not significantly associated with locoregional control ($P = .11$), distant metastases-free survival ($P = .32$), or overall survival ($P = .07$).

Conclusion: A prolonged DTI did not appear to adversely affect outcomes in this cohort of patients with LAHNC.


Physicians and patients are often concerned regarding any prolonged treatment delay from the time of diagnosis of a squamous cell carcinoma of the head and neck. This concern stems from the belief that delays allow the growth of the local tumor and increase the likelihood of distant metastases. Clearly, delays that exceed a certain threshold will eventually result in progression.

Patients with locoregionally advanced head and neck cancer (LAHNC) often present with many baseline difficulties that require social, dental, and nutritional interventions. Also, the treatment planning process for these complex tumors may take longer than that for other tumors. This process has become increasingly complex with the advent of treatment planning procedures that may include the fusion of magnetic resonance or positron emission images with computed tomographic (CT) images. Furthermore, the complexities associated with intensity-modulated radiotherapy (IMRT) may cause delays in the start of radiotherapy.

Some retrospective studies suggest that relatively short delays in the initiation of radiotherapy may be associated with increasing tumor bulk and with decreases in local control for a variety of cancers, including head and neck cancer.1,2 In a study of 61 patients with a diagnostic CT scan followed by a radiotherapy treatment planning CT scan usually weeks later, Jensen et al3 found that 30% had progressive disease on the treatment planning CT scan by Response Evaluation Criteria in Solid Tumors criteria, 62% had any measurable increase, 20% developed new lymph node metastases, and 16% showed progression in TNM classification. This progression may then be associated with decreased probability of local tumor control.3-5 Two studies examining this question found decrements in outcomes with greater waiting times.6,7 Two other studies showed a nonsignificant trend supporting the hypothesis that longer waiting times result in inferior outcomes,8,9 although one study showed no association.10 In a systematic review of these retrospective data, Huang et al11 showed that there was a strong trend ($P = .06$) toward reduced local control with a 1-month (30-day) delay in radiotherapy. These prior findings suggest that tumor bulk or radioresistance increases with increasing diagnosis-to-treatment interval (DTI), thereby hindering the effect of radiotherapy. However, most of these data were from cases involving patients with early-stage head and neck cancer. Therefore, we sought to assess whether the DTI affected outcomes in cases involving patients with LAHNC.
Methods

Seven hundred eighty-one patients with squamous cell carcinoma of the head and neck (larynx, hypopharynx, oropharynx, oral cavity, nasopharynx, nasal cavity, paranasal sinus, or unknown primary site) treated with radiotherapy from 1995 to 2007 were identified in a database at the University of Alabama at Birmingham. Patients were excluded if they had undergone prior treatment for head and neck cancer (eg, definitive surgery, neck dissection, or chemotherapy), were younger than 18 years, had stage I or II tumors, or had been treated palliatively. The characteristics of the 427 patients remaining for analysis are listed in Table 1.

The DTI was defined as the time in days between the date that a biopsy specimen demonstrated malignancy and the first day of radiotherapy. The Karnofsky Performance Status (KPS) was interpreted based on the patient’s condition at the initial consultation if one was not recorded in the chart. The treatment characteristics are also listed in Table 1. All patients were immobilized with a thermoplastic head and neck mask and then underwent CT simulation. Their treatments were planned using commercially available treatment planning systems (Eclipse; Varian Medical Systems Inc, Palo Alto, California) was used after 2002. The Mann–Whitney U test was used to determine if the median DTI differed between groups. The univariate and multivariate analyses were performed using multivariate regression analysis. The data were analyzed using SPSS version 16 (SPSS Inc, Chicago, Illinois).

The median follow-up of patients alive at last contact was 51.5 months. The median DTI was 34 days (range, 7–94 days; interquartile range, 24–50 days). The mean DTI was 43.09 days (95% confidence interval [CI], 39.46–46.72). Factors associated with a longer than median DTI included primary site (P=.01), African American ethnicity (P=.004), lower KPS (P=.004), treatment off protocol (P=.002), insurance type (P<.001), and use of IMRT (P<.001) (Table 1).

On regression analysis, lower KPS (P<.001), use of IMRT (P>.001), and insurance type (P=.001) remained significantly associated with a DTI of greater than 34 days (Table 2). The patients whose health coverage was through the Department of Veterans Affairs, Medicaid, or charity care had a longer DTI than those who were
covered through commercial insurance or Medicare. A longer DTI was not significantly associated with LRC (P = .12), DMFS (P = .24), or OS (P = .14) (Figure 1). Even when the lowest quartile (≤24 days) was compared with the highest quartile (>51 days), there was no significant difference in LRC (P = .22) or OS (P = .47) (Figure 2).

As a continuous variable, the DTI was not associated with LRC (P = .10; odds ratio [OR], 1.003; 95% CI, 0.999-1.007), or DMFS (P = .97; OR, 1.000; 95% CI, 0.992-1.008) on regression analysis. The DTI as a continuous variable was associated with OS (P = .03); however, the OR was small at 1.003, and the 95% CI did encompass unity (1.000-1.006) and was no longer significant on multivariate Cox regression analysis (P = .26; OR, 1.002; 95% CI, 0.999-1.005).

Delay to cancer treatment has been shown to reduce patient-reported satisfaction. In this study, the use of IMRT, with its inherent added complexity, including CT simulation, fusion of other imaging studies, contouring, treatment planning, and quality assurance, was most strongly associated with a prolonged DTI, with an OR of 3.5 (95% CI, 2.17-5.67). Also, patients without health insurance or with insurance through Medicaid or the Department of Veterans Affairs were more likely to have a longer DTI than patients with commercial health insurance or Medicare (Table 1 and Table 2). This finding may be attributable to logistical difficulties inherent in the institutional referral process, as radiotherapy services are provided at a different hospital than these sources of referral. Patients with a higher KPS were more likely to have a shorter DTI (OR, 0.62; 95% CI, 0.40-0.96), likely reflecting the ability to handle any additional medical interventions, such as dental, nutritional, or social, required prior to the initiation of radiotherapy. These patients are likely more amenable to multiple appointments within

Figure 1. Impact of diagnosis-to-treatment interval (DTI) on cancer control outcomes. A, Locoregional control. B, Distant metastases-free survival. C, Overall survival. The median DTI was 24 days.

Figure 2. Impact of diagnosis-to-treatment interval (DTI) by quartiles on cancer control outcomes. A, Locoregional control. B, Overall survival.
a short time frame, as preparation for LAHNC treatment often requires a busy schedule. Streamlining the IMRT treatment planning process and ancillary services for patients with poor KPS as well as the referral process of patients with certain types of health insurance may improve the time between diagnosis and treatment, which in turn may result in improved patient-centered outcomes related to patient satisfaction and quality of life.

Previous studies suggest that many patients with head and neck cancer may present at a time of rapid growth, and delays could increase the target volumes and potentially diminish LRC. However, the results of the present study did not confirm this hypothesis, although there were trends suggesting that prolonging the DTI could be detrimental. In this large group of patients with LAHNC who were treated with primary radiotherapy, the median DTI was 34 days, as compared with a range of 15 to 43 days reported in the literature. Therefore, differences in the DTI are unlikely to explain the results. Whereas prior studies of DTI focused on early-stage head and neck cancer,6-10 the present study included only LAHNC. Potentially in this population of relatively larger tumors, the growth fraction could be lower or the cell loss factor could be higher, resulting in a comparatively longer population-doubling time and a reduced sensitivity to delay.

Alternatively, it is possible that as the incidence of human papillomavirus (HPV)-associated LAHNC has increased, the significance of progression prior to treatment has decreased.11,12 For example, in a recent publication from the Radiation Therapy Oncology Group, a subgroup of HPV-positive patients had a 3-year OS of 93% after concomitant cisplatin therapy and radiotherapy.13 With such results for the HPV-positive population, the possible significance of delays for the HPV-negative population may have been diluted. Unfortunately, we currently do not have data regarding HPV for this cohort, and we are unable to test this hypothesis at this time.

Most information supports the concept that timely initiation of therapy is a laudable approach. However, the results reported herein suggest that complex cases may require additional planning procedures, and these delays, which are aimed to improve the treatment, are unlikely to cause detrimental effects. Furthermore, the recent technologic advances in radiotherapy continue to evolve, and the processes are expedited compared with the recent past. It is important to develop a system in which patients who need to travel great distances can undergo multiple aspects of planning during a single trip.

In the future, it may also be helpful to assess the time from the onset of symptoms to the initiation of radiotherapy. A group in Denmark has also found this time parameter to be of significance when examining tumor control probabilities.14 However, such an assessment may be difficult as it is based on patient memories and could be inaccurate. Stratifying patients based on HPV status may also identify higher-risk subgroups that may also be more sensitive to radiotherapy delays. Finally, it is possible that stratifying patients based on doubling time, as calculated between the diagnostic CT and the radiotherapy planning CT, may identify those patients who are more or less susceptible to adverse outcomes because of radiotherapy delays.

Submitted for Publication: June 29, 2010; final revision received September 29, 2010; accepted October 21, 2010.

Correspondence: Jimmy J. Caudell, MD, PhD, Department of Radiation Oncology, University of Mississippi Medical Center, 350 Woodrow Wilson Dr, Ste 1600, Jackson, MS 39213 (jjcaudell@gmail.com).

Author Contributions: Dr Caudell had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Caudell and Bonner. Acquisition of data: Caudell and Bonner. Analysis and interpretation of data: Caudell, Locher, and Bonner. Drafting of the manuscript: Caudell and Bonner. Critical revision of the manuscript for important intellectual content: Caudell, Locher, and Bonner. Statistical analysis: Caudell and Locher. Administrative, technical, and material support: Bonner. Study supervision: Caudell and Bonner.

Financial Disclosure: Dr Bonner is an occasional consultant for, and has received honoraria from, Bristol-Myers Squibb Company, ImClone Systems Inc, Eli Lilly and Company, Oncolytics, Sanofi-Aventis, and AstraZeneca. He is also on the Speaker’s Bureau of Bristol-Myers Squibb Company.

Previous Presentation: This study was presented in part at the Multidisciplinary Head and Neck Cancer Symposium; February 26, 2010; Chandler, Arizona.

REFERENCES