Factors Associated with Adjuvant Treatment Delays in Patients Treated Surgically for Head and Neck Cancer

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Abstract

Objectives: To determine the patient and treatment characteristics associated with delay in post-operative radiation therapy (PORT) for patients treated surgically for head and neck squamous cell cancer (HNSCC) at our institution. Design: Single institution retrospective review Setting: Tertiary care academic medical center Participants: Patients treated surgically for HNSCC that underwent PORT between 2013-2016 Main outcomes measures: Time from surgery to initiation of PORT. Results: 140 patients met inclusion criteria. A majority did not start radiotherapy within six weeks. Factors associated with a delayed initiation of PORT included length of stay >8 days, 30-day readmission, no adjuvant chemotherapy, post-operative complications, and fragmented care. Conclusion: A majority of patients did not initiate PORT within the guideline-recommended 6 weeks. Modifiable risks factors that delay initiation of PORT were identified.

Introduction

Head and neck squamous cell carcinoma (HNSCC) often requires multimodality treatment including surgery, radiation therapy, and chemotherapy. For patients treated surgically for HNSCC, the National Cancer Comprehensive Cancer Network (NCCN) Treatment Guidelines recommend the initiation of post-operative adjuvant radiation therapy (PORT) within six weeks of surgery.[1] In fact, timely initiation of post-operative radiation is the only measure of timely care incorporated into the NCCN guidelines for HNSCC.

This recommendation originates from studies that found improved overall survival when adjuvant treatment was initiated within six weeks of surgery.[2-5] More recently, Graboyes et al[6] conducted a National Cancer Data base review, which identified 41,291 patients requiring PORT, to reevaluate these recommendations. This analysis supported the guidelines, as delays in initiating PORT beyond 6 weeks after surgery was associated with a 10% absolute decrease in overall survival.[6] With a push towards healthcare related quality improvement, adjuvant radiation therapy within six weeks has been identified as a quality metric that has a meaningful impact on survival.[7]

Despite the NCCN guideline recommendations, a majority of patients do not initiate PORT within six weeks. In a separate paper, Graboyes et al, found that only 44.7% of patients initiated PORT within six weeks of surgery. Of additional concern, it appears the proportion of patients experiencing delays is on the rise.[8]

Risk factors associated with delayed initiation of PORT include patient-, tumor-, and treatment-specific characteristics.[8-15] Factors implicated in delayed initiation of PORT include black race, public or no insurance, lower level of education, increasing severity of comorbidities, increased postoperative length of stay, 30-day unplanned readmissions, and undergoing surgery and PORT at different facilities, i.e. "fragmented care."

In this study, we sought to identify modifiable risk factors associated with delayed initiation of PORT and implement process-related quality improvement metrics to address those factors. Improving compliance to guideline recommendations for timely initiation of PORT would be expected to improve overall survival.

Materials and Methods

After obtaining approval from the Institutional Review Board, a case-series reviewing patients treated surgically for squamous cell carcinoma of the upper aerodigestive tract at our academic institution who then underwent post-operative radiation therapy between 2012 and 2016 was conducted. Due to the retrospective nature of this study, consent was waived. A database of head and neck cancer patients treated at INSTITUTION BLINDED FOR REVIEW during these years was used to identify individuals who met the criteria for the study.

Patients were included if over eighteen years of age at the time of surgery, a pathology-confirmed diagnosis of squamous cell carcinoma, primary surgical resection at INSTITUTION BLINDED FOR REVIEW, and the need for PORT following primary resection. Patients who underwent induction chemotherapy prior to surgery, those who received salvage surgery following prior treatment with radiation therapy, and patients who declined recommended PORT were excluded from the study.

After identifying subjects through the database, data points on patient demographics, pathology reports, surgery, and treatment characteristics were collected. Patient demographic characteristics included: age, gender, race, insurance status, alcohol use, and tobacco use. Pathology characteristics included: primary tumor site, TNM staging, human-papillomavirus (HPV) status, and any recurrence as diagnosed by biopsy, imaging, or clinical diagnosis. Surgery characteristics included: surgery date, discharge date, post-operative length of stay greater than or equal to eight days, post-operative complications (including wound complications, wound infections, pneumonia, or need for repeat operation), readmissions within thirty days of surgery, post-operative rehabilitation center admission, post-operative dental extractions, and post-operative feeding tube placement. Finally, adjuvant therapy characteristics included: history of prior head and neck cancer treatment, facility location of adjuvant therapy, need for concurrent chemotherapy, date of first and last radiation session, days to initiation of radiation from surgery, prescribed number of radiation fractions, completed number of radiation fractions, prescribed number of chemotherapy treatments, and completed number of chemotherapy treatments.

We utilized available scanned treatment reports in our electronic medical record for patients who received adjuvant therapy at outside institutions. Facilities were contacted if this information was incomplete or missing from the record and updated accordingly.

Descriptive statistics, including frequencies and proportions for categorical variables and means, standard deviations, medians, 25^{th} and 75^{th} percentiles for continuous measures, were calculated for all measures of interest. Non-parametric tests (Wilcoxon Two-Sample Test and Kruskal-Wallis Test) were used to test for differences in continuous measures among study groups, while Fisher's Exact Test was used to test if the measure was categorical. The Kaplan-Meier method was used to estimate delays in treatment; Cox Proportional Hazards models were used to assess the association between delays and study measures in both univariate and multivariate models. P-values < 0.05 were considered to be statistically significant; SAS (version 9.4, Cary, NC, USA) was used for all analyses.

Results

302 patients were identified. Patients were excluded for the following reasons: no adjuvant therapy recommended (n=140), declined post-operative therapy (n=23), patient died before adjuvant therapy could begin (n=7), additional therapy was palliative and/or the patient moved in to hospice care (n=5), and lost to follow up (n=3). 124 patients met inclusion criteria (Table 1). The patient demographic information is presented in Table 1. Most patients were >50 years old, male, white, and smokers. There were a variety of payer types, with the highest proportion being privately insured (44.4%).

The median number of days from surgery to initiation of PORT in these patients was 55.5 days (7.9 weeks). 11.4% of patients began PORT within 42 days or fewer.

Statistically significant factors for increased interval from surgery to initiation of adjuvant therapy include post-op length of stay greater than or equal to eight days (p = 0.01, mean difference of 6.9, (95% CI of -0.9, 14.8 days)), readmission within 30-days of surgery (p = 0.045, mean 13.1, (0.9, 25.4), no adjuvant chemotherapy post-operatively (p = 0.0087, mean 7.9 (0.1, 15.7), post-operative complications (p = 0.011, mean 7.1 (-0.8, 15.1), and fragmented care (p = 0.018, mean 11.4, (4.4, 18.4).

Figures 1 through 4 depict the proportion of patients who initiated adjuvant therapy over time for selected risk factors. Figure 1 depicts the delays in initiation of therapy in association with fragmented care. For those receiving fragmented care, a greater proportion of patients had not yet started therapy as the post-operative date increased. Figure 2 depicts the delay demonstrates the delays in post-operative radiation therapy associated with increased hospital length of stay after surgery. Figure 3 depicts the delays in initiation of therapy in association with concurrent therapy. For patients receiving adjuvant chemotherapy, a greater proportion of patients had initiated therapy as the post-operative date increased.

Admission to a rehabilitation center after surgery, the need for dental extractions, and the need for a feeding tube placement showed a delay in initiation, but were not statistically significant. Tumor pathology and primary site did not show a statistically significant delay to initiation of treatment (Table 2).

Conclusions

A quality gap exists between national guideline recommendations and delivery of post-operative radiation therapy in patients treated surgically for HNSCC. A majority of patients do not initiate post-operative radiotherapy within guideline-recommended 6 weeks.[8] Our single academic institution review mirrored those results. The majority of patients (88.6%) did not start RT within 6 weeks of surgery, and the average time to initiate of PORT was 7.9 weeks.

Risk factors for a delay in initiation of PORT include, but are not limited to, lower seriocomic status, black race, public insurance, or uninsured, increasing severity of comorbidities, increased post-operative LOS, 30 day readmissions, fragmented care[8], and receiving adjuvant therapy at a non-academic center.[10,15]

Our case-series sought to determine potentially modifiable risk factors which are associated with a prolonged initiation of PORT. Many patient related factors that might delay PORT cannot be altered - such as patient age or tumor stage at presentation. However, there exists some patient and treatment related factors which offer an opportunity for quality improvements and thus earlier initiation of PORT. While previous studies have identified several factors associated with a delay in PORT, our study assessed additional potentially modifiable risk factors such as gastrostomy tube placement, rehabilitation facility placement, and post-operative complications which were all associated with, or at least showed a trend towards, a delay in PORT (Figure 4). Additionally, our single-institution study allows for collection of these more granular data points (such as wound complications and infections), which may not be available in the larger database studies.

Post-operative length of stay, 30-day readmission and post-operative complications were associated with delays. Interestingly, patients who received adjuvant chemotherapy had significantly lower intervals between surgery and initiation of adjuvant therapy (10 days fewer, p = 0.087). Additionally, delays were decreased if surgery and adjuvant radiotherapy were performed at the same institution. Need for dental extractions, gastrostomy tube placement, and rehabilitation facility placement were associated with a longer interval to initiation of PORT, but were not statistically significant.

The finding that the addition of adjuvant chemotherapy to radiation was associated with earlier initiation of adjuvant therapy seems counterintuitive. We postulate that the reduced interval for these patients may be due to earlier recognition for needed adjuvant therapy. A patient with more advanced clinical disease at initial presentation may be referred in a timelier fashion than a patient whose need for adjuvant therapy may be unclear at initial presentation. Referrals in the latter type of cases are typically made only after final pathology results are released, and perhaps only after a tumor board discussion; this decision may not

occur until up to 2-3 weeks after surgery. However, this finding may be in part explained by the fact that adjuvant chemotherapy is only be offered to a healthier subset of patients. These patients would be more likely to start therapy sooner than their unhealthy counterparts.

Fragmented care has previously been associated with delayed initiation of PORT and poor adherence to treatment regimens,[10]and poorer outcomes.[16,17] We found a statistically significant decrease in PORT delays for those who received both surgery and adjuvant therapy at our academic facility. Academic centers may improve timeliness of care due to ease of intra-institutional referrals, care coordinators, and multidisciplinary tumor boards which include surgeons, radiation, and medical oncologists. Additional benefit may include the patient volume of an academic center,[17]higher level of comfort with management of HNSCC-related complications, and fewer treatment interruptions or early terminations. Adjuvant therapy at an academic center has also been shown to reduce total "package time" (time from surgery to completion of adjuvant therapy), likely for the reasons stated above. A reduction of package time is associated with increased overall and recurrence free survival.[14-15] This difference in fragmented vs. unfragmented care may be patient related as well. Those who choose to continue their adjuvant therapy at our institution, often despite significant commutes, may be more motivated, educated, have better family support, or better access to transportation.

Improving adherence rates for all patients will be challenging, as there are often unavoidable delays that push initiation of PORT beyond 6 weeks. Therefore, it is critical to identify those modifiable factors which may be contributing to PORT delays and directly address those factors through quality improvement processes.

Divi et al[12] demonstrated the utility of a structured quality improvement project in decreasing the time from surgery to initiation of adjuvant therapy. Twelve interventions which sought to address the three key drivers of delay (delayed dental extraction, delayed referral to radiation oncology, and poor patient or team engagement) were implemented. They noted a reduction in avoidable delays from 24 to 9%. Additionally, Janz et al[13]demonstrated the following care processes improved timeliness of PORT: preoperative RT consultation, pathology report available within 7 days of surgery, time from surgery to PORT referral no longer than 10 days, and time for PORT consultation to its start no longer than 21 days.

In this study, we also noted that patients with longer LOS and those who had postoperative complications had significant delays in initiating adjuvant therapy. This presents an opportunity for intervention. The patients who are at risk for longer stays (e.g. those requiring free flap reconstruction, those without caregivers at home) or who are at high risk for complications (e.g., those with multiple comorbidities) should be identified and preoperative referrals to adjuvant care providers can be made. If the need for G-tube placement[18] or dental extractions can be anticipated, these can be accomplished pre- or intra-operatively. However, complications and length of stay are not always modifiable factors, as unforeseen events often unfold during patients' post-operative course, which may not be predicted. For example, a patient without significant comorbidities may still develop a wound complication which would prolong their stay.

We have initiated a structured institutional multidisciplinary process at our institution in hopes of reducing delays. This initiative will generate automated referrals and include a checklist led by a Head and Neck Cancer-specific nurse navigator to identify at-risk patients, facilitate consult appointments, review of pathology reports, and ensure timely presentation at tumor board. The specific details of the initiative are currently in development in conjunction between our surgeons, radiation oncologists, medical oncologists, and nurse navigator.

There were limitations to this study. Our sample size was adequate to determine statistical significance in delay for several risk factors. However, some risk factors (gastrostomy tube placement, need dental extractions, rehabilitation facility placement) showed a trend towards delay, but were not statistically significant, as might have been expected from prior studies.[8]

There was also a lack of availability of some outside treatment facility records, which resulted in exclusion of those patients. Some records did not include the day of therapy initiation, number of fractions received, number of fractions completed, or total treatment dose.

Our single academic institutional study also makes the results challenging to generalize to those not practicing in a similar setting.

Finally, comparing all non-academic centers as a single aggregate to our academic institution may unfairly generalize their outcomes. It is possible some non-academic centers have better outcomes than others, or even our institution, but this was not assessed in the data.

This study is important because it identifies modifiable risk factors for a delay in initiation of PORT, a known metric for quality care in HNSCC. Future studies will address the success of a structured institutional multidisciplinary approach and the use of a dedicated nurse navigator in reducing delays in adjuvant therapy, and assessing its effect on outcome measures, such as recurrence rate and disease-free survival in HNSCC.

In this single institution case series, a majority of patients with HNSCC did not adhere to recommendation of initiating adjuvant radiotherapy within 6 weeks of surgery. Identification of modifiable risks factors/barriers that delay initiation of PORT is crucial to reduce avoidable delays. A structured quality improvement project, which directly addresses these modifiable risk factors, would be expected to improve guideline recommended adherence to post-operative RT time intervals, and ultimately improve survival outcomes in patients with HNSCC.

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Patient Variable	**No. of patients (%)**
Age	
<50	19 (15.3)
50-59	44 (35.4)
60-69	34 (27.4)
>70	27 (21.8)
Gender	
Male	96 (77.4)
Female	28 (22.6)
Race	
White	113 (91.1)
Black	6 (4.8)
Hispanic	1 (0.8)
Other	4 (3.2)
Insurance Type	
Private	55 (44.4)
Medicaid	27 (21.8)
Medicare	25 (20.2)
Medicare Disabled	10 (8.1)
Alcohol Use	
Never	70 (56.9)
Occasional	27 (22.0)
Heavy	26 (21.1)
Tobacco	
None	30 (24.2)
Cigarettes	70 (56.5)
Smokeless	8 (6.5)

Both	16 (12.9)
ASA	
2	24 (19.3)
3	91 (73.4)
4	9 (7.3)

Table 1 : Patient demographics.

	n	**Days to Initiation, Median (p25-p75)**	**p-value**
Overall	124	55.5 (47-73.0)	
Post-op LOS			0.01
< 8 days	64	51 (45-69.5)	
[?] 8 days	60	58.5 (52-74.5)	
Post-op complication			0.01
Yes	29	64 (54-75)	
No	95	53 (46-70)	
Post-op readmission			0.05
Yes	14	66 (53-91)	
No	110	55 (47-70)	
Rehab admission			0.21
Yes	5	65 (55-74)	
No	119	55 (47-73)	
Need for dental extractions			0.12
Yes	38	58.5 (52-75)	
No	85	53 (47-71)	
Feeding tube placement			0.11
Yes	34	60.5 (48-88)	
No	47	52 (47-59)	
Fragmented care			0.02
Yes	77	62 (48-75)	
No	47	52 (47-59)	
Concurrent chemotherapy			0.01
Yes	65	53 (47-65)	
No	59	63 (49-75)	
T stage			0.75
1	25	58 (49-70)	
2	33	52 (48-66)	
3	24	55 (47.5-69)	
4	40	56 (49.5-75)	
N stage			0.20
0	43	58 (49-70)	
1	20	54 (47-73.5)	
2	59	53 (47-73)	
3	3	34 (30-55)	
HPV status			0.69
Positive	30	52 (47-73)	

Negative	94	56 (48-70)	
Primary Tumor site			0.19
Oral cavity	58	55.5 (46-69)	
Oropharynx	32	53 (49-72)	
Hypopharynx	7	52 (47-92)	
Larynx	20	68 (50.5-78)	

Table 2 : Factors associated with a delay in PORT. PORT, post-operative radiation therapy

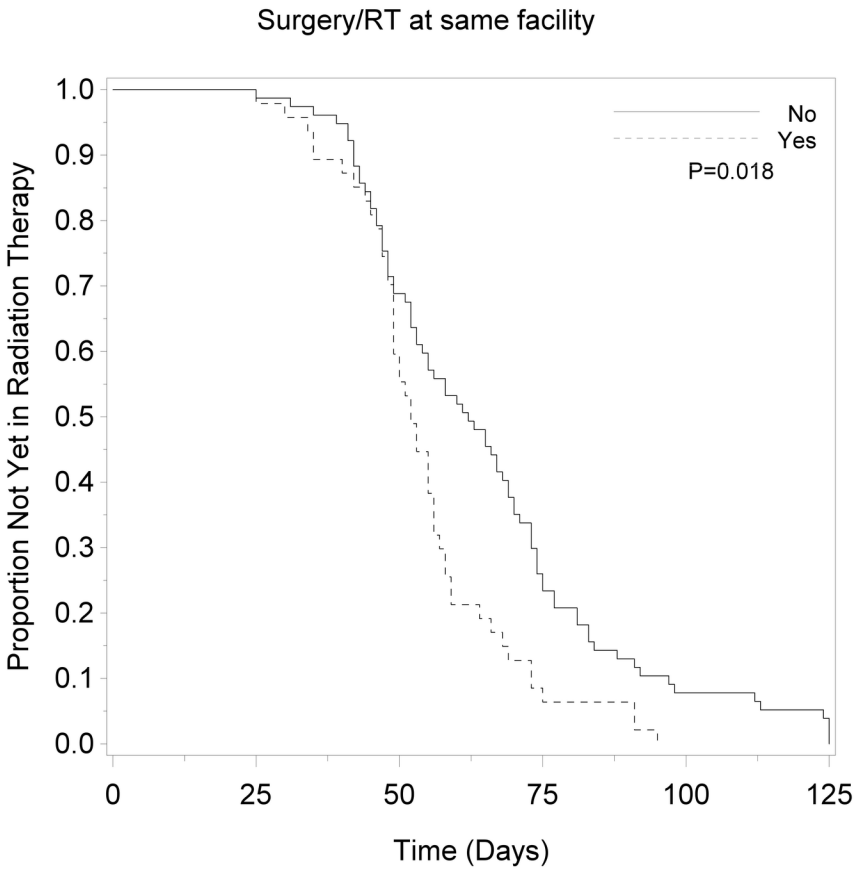

Figure 1 : Delays in PORT initiation associated with fragmented care.

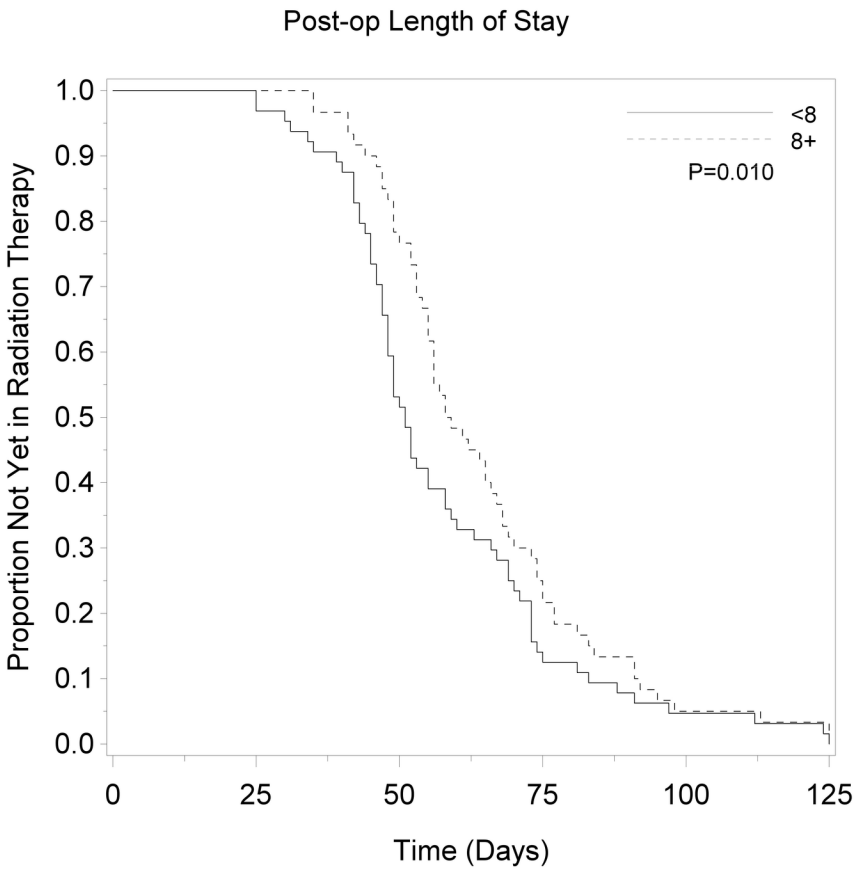

Figure 2 : Delays in PORT initiation associated with length of stay.

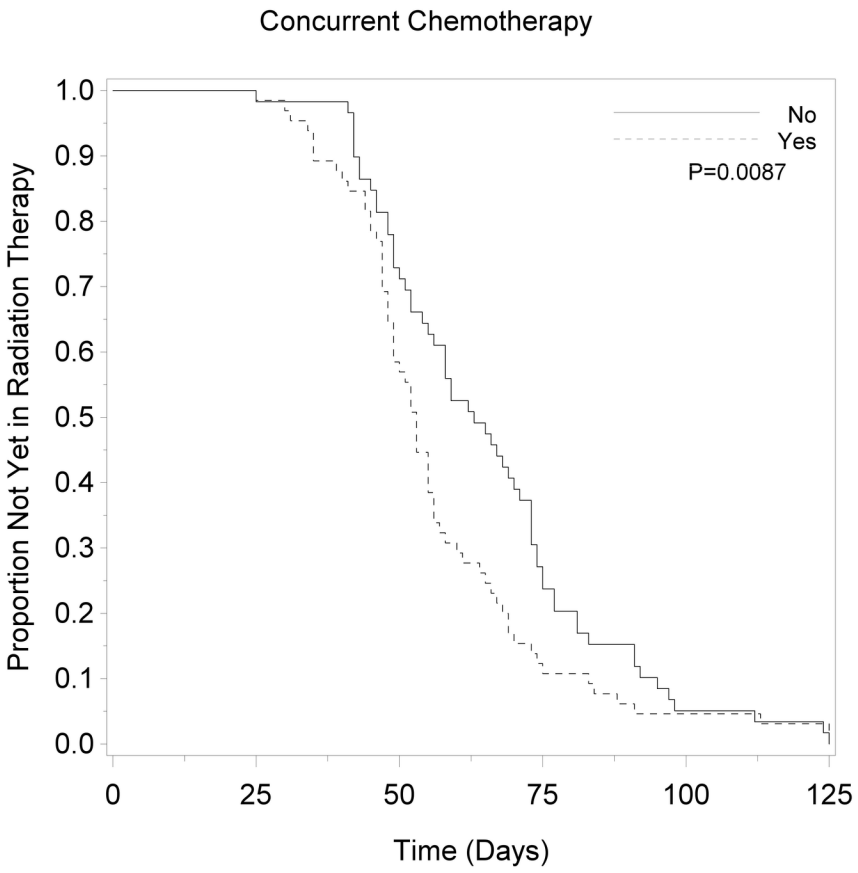

Figure 3: Shorter time to PORT initiation associated with concurrent chemotherapy.

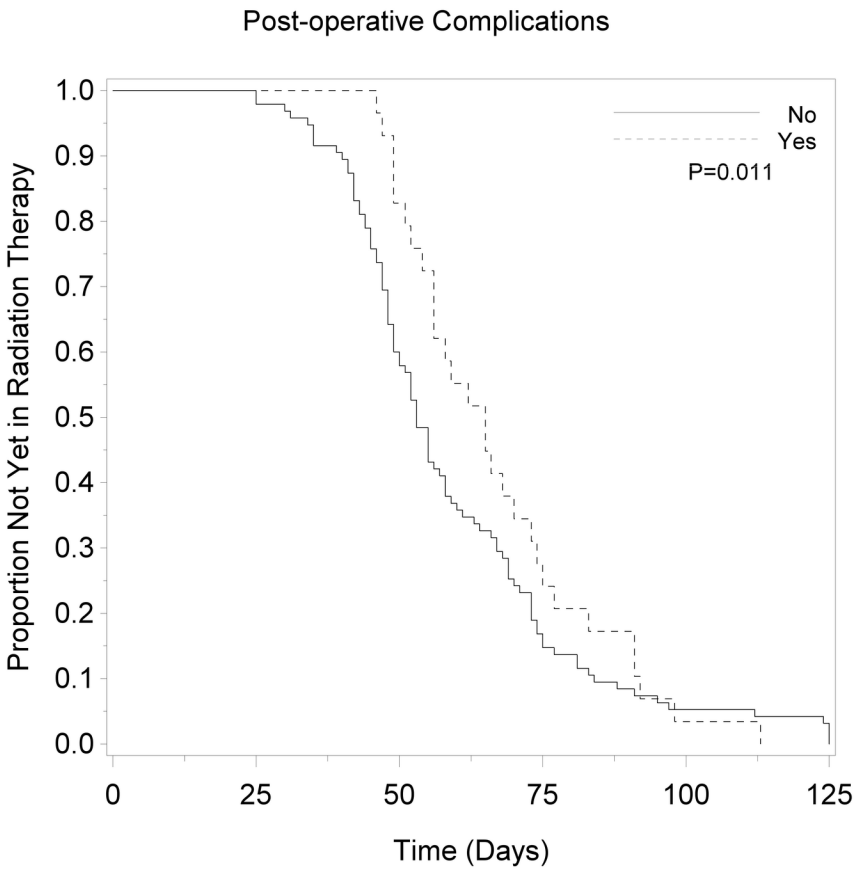

Figure 4: Delays in PORT initiation associated with post-operative complications.