Title

Proactive Risk-based Optimization & Notifications for Treatment & Outcomes in Head & Neck Cancer (PRONTO-HN): A Strategy to Reduce Delays from Surgery to Post-Operative Adjuvant Therapy in Head and Neck Cancer

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1. Summary of the Research ProtocolRationaleThe optimal management of head and neck cancer requires a multidisciplinary approach. Delays in treatment intervals, particularly between surgery and post-operative radiotherapy (S-PORT) have been associated with reduced overall survival. Preliminary studies by our team have shown that treatment delays are highly prevalent in Canada.

1.2. Primary ObjectiveTo evaluate the impact of enhanced care coordination and an automated alert system on S-PORT delays in patients with head and neck cancer requiring multimodal therapy.

1.3. Primary EndpointProportion of patients with S-PORT ≤ 42 days.

1.4. Secondary and Tertiary EndpointsOverall survival (OS)

- Locoregional survival (LRS)
- Distant metastasis-free survival (DMFS)
- Disease-free survival (DFS)
- Recurrence-free survival (RFS).

1.5. Study DesignA single-center, quasi-experimental interrupted time-series pilot study. Phase 1: Group A (control) – pre-implementation of the PRONTO-HN system. Phase 2: Group B – following implementation of the PRONTO-HN system.

1.6. Study PopulationPatients with oral cavity or laryngeal squamous cell carcinoma treated with primary intention surgery at the CHUM.

1.7. Data Collection: Variables and MeasuresOur newly developed organizational navigation system optimizes multidisciplinary team coordination by extracting data from hospital systems and sending automatic task-specific reminders and deadlines. Risk stratification is performed using our validated pre-operative predictive model for adjuvant therapy need.

1.8. Study Conduct and Data QualityTo minimize seasonal bias, both study phases span 12 months.

1.9. Taille d'échantillonWe estimate that 80 patients per year are treated with primary intention surgery at the CHUM for oral cavity or laryngeal squamous cell carcinoma. To demonstrate a reduction in S-PORT delays from 80% to 50% (α=0.05, β=0.20), a sample size of 38 patients per group is needed.

1.10. Study duration- Control phase: August 2024 – August 2025
- Intervention phase: September 2025 – September 2026

1.11. Statistical AnalysisThe statistical analysis will be performed using R statistical software. Patient characteristics will be presented as means (standard deviation) or medians (interquartile range) for continuous variables, and frequency distributions (number and proportion) for categorical variables. Univariate logistic regression will identify covariates associated with prolonged treatment intervals. Multivariate logistic regression will explore the independent association between the

intervention and treatment intervals, using a combination of univariate regression, expert opinion, and variables known from the literature to be associated with treatment delays.

2. Introduction

2.1. *Study rationale* The optimal management of head and neck cancers often requires a multidisciplinary approach. Several treatment intervals have been described in the head and neck cancer literature, including the diagnosis and treatment interval (DTI), surgery to post-operative radiation therapy (S-PORT), and radiation therapy interval (RTI). Delays in these intervals could negatively impact oncological outcomes and overall survival [1-10].

In a Canadian multicenter study, our team demonstrated an association between SPORT delays and oncological outcomes in oral cavity cancer patients, with a reduction of approximately 10% in 3-year overall survival [3]. Motivated by these findings, our group conducted a subsequent study to identify predictors and organizational bottlenecks causing delays in treatment intervals [11]. We found that time to pre-operative imaging report was associated with prolonged DTI and times to pathology report, to maxillofacial consult and to medical oncology consult were associated with prolonged SPORT. Strategies targeting these organizational bottlenecks may be effective for shortening treatment time intervals, hence representing potential opportunities for improving oncological outcomes in head and neck cancer patients. In another follow-up study, our team developed a predictive model using pre-operative data for necessitating adjuvant therapy after surgery in this patient population [12].

2.2. *Background* The National Comprehensive Cancer Network (NCCN) Guidelines for head & neck cancer recommend initiating post-operative radiation therapy within 6 weeks after surgery [13]. In a recent systematic review and meta-analysis of studies conducted in the United States of America, Duckett et al found that delays in initiating PORT within recommended delays occurs in approximately 50% of patients [14]. Similarly, in our Canadian multicenter study, we had found that it was nearly 80% of patients who have prolonged S-PORT interval [3].

This field of research is very quickly growing. The focus is shifting from reporting the prevalence of treatment delays and its association with outcomes in head and neck cancer to comprehending the obstacles and developing interventions to tackle them. Still, there is limited research exploring interventions aimed at reducing treatment delays in head and neck cancer.

Qualitative interview-based studies have identified various obstacles potentially impeding the prompt completion of SPORT. These barriers include poor patient education about SPORT, suboptimal care coordination and communication among members of the multidisciplinary team, travel challenges, inadequate social and financial support, and process delays [15,16]. Through chart reviews and departmental discussions at their institution, Divi et al postulated that timely dental extraction, referrals to radiation oncology and medical oncology, and patient engagement were important drivers of SPORT [17]. They then proposed twelve interventions aiming to reduce treatment delays. These interventions include dental Panorex at new visits, having a coordinator for adjuvant therapy consults, early discussions with patients of where adjuvant therapy will take place, etc. After implementing these measures (N=56), the percentage of patients completing SPORT in under 42 days went from 62% (21/34) to 73% (16/22), though statistical significance was not reported. In another study, Graboyes et al (N = 15) implemented a comprehensive intervention involving patient education, travel support, care plans, referral tracking, and organizational restructuring [18]. They demonstrated the feasibility and acceptability of the intervention, with 86% of patients in their cohort completing S-PORT in 42 days or less.

2.3. *Benefits and risks*The current study proposes an organizational intervention to improve treatment delays for patients with head and neck cancer. Given the increasing amount of evidence that prolonged treatment times have a negative impact on overall survival in head and neck cancer patients and the fact that most patients in North America do not adhere to recommended treatment times [3,19,20], if this study were to be successful it has the potential to improve oncologic outcomes in this patient population. Other benefits include improved patient experience. Conversely, the proposed study poses no risk for patients. The proposed intervention will help healthcare team providers improve collaboration, communication, and coordination, but will not directly impact the patient or change the therapeutics received by the patient.

3. *Objectives and endpoints*

3.1. *Primary objective*The primary objective is to evaluate the impact of an organization navigation, care coordination, risk stratification and automated physician alert system on S-PORT delays in patients with head & neck cancer requiring multimodal therapy.

3.2. *Secondary objectives*The secondary objective is to evaluate the impact of an organization navigation, care coordination, risk stratification and automated physician alert system on overall survival, locoregional survival, distant metastasis-free survival, recurrence-free survival and disease-free survival time in patients with head & neck cancer requiring multimodal therapy.

3.3. *Primary endpoint, primary outcome measure*Surgery to post-operative radiation therapy (SPORT - defined as number of days from surgery to initiation of radiation therapy or chemoradiation) ≤42 days.

- S-PORT mean

3.4. *Secondary, tertiary / exploratory endpoints*Oncologic outcomes all defined from time to surgery to time of event.

- Overall survival, with events defined as death from any cause.
- Locoregional survival, with events defined as locoregional recurrence (primary site or cervical node) or death.
- Distant metastasis-free survival, with events defined as distant metastasis or death.
- Recurrence-Free Survival, with events defined as any recurrence (local, regional, or distant). Deaths without recurrence are censored.
- Disease-free survival, with events defined as recurrence (any site) or death.

4. *Methods*

4.1. *Study design and context*A single center quasi-experimental interrupted chronological series pilot study will be used to evaluate a new care coordination intervention (detailed below).

The study will be divided into two phases: firstly, as a control group, consecutive pre-intervention eligible patients will be included in Group A. The treatment time intervals will be extracted registered from a prospectively maintained database for all cases in Group A (from August 2024 to August 2025). In the second phase, the new care coordination system (detailed below) will be introduced (starting September 2025 until September 2026). Consecutive eligible patients in this phase will be included

in Group B. The treatment time intervals will be prospectively registered for all cases in Group B. The study will be performed using an intention-to-treat analysis. Individual patient data will be collected.

4.2. *Study population*Patients with oral cavity and laryngeal squamous cell carcinoma treated with primary intention surgery.

4.2.1. *Inclusion criteria*

- All adult patients (age 18 or greater).
- Pathologically confirmed oral cavity or laryngeal squamous cell carcinoma.
- Diagnosed from August 2024 to August 2026.
- With planned primary intention surgical resection from August 2024 to September 2026.
- Treated at the Centre Hospitalier de l'Université de Montréal.

4.2.2. *Exclusion criteria*

- Patients who do not end up receiving surgery.
- S-PORT > 180 days

4.2.3. *Participant selection or recruitment*Patients from the pre- and post-intervention groups come from the same cohort. Patients will be identified at time operative request is made by head and neck surgeon (Division of Otolaryngology, Centre Hospitalier de l'Université de Montréal). All eligible patients meeting the inclusion and exclusion criteria will be enrolled in the study. The investigation involves a quality improvement intervention designed to enhance the organization and healthcare administration for the head and neck oncology multidisciplinary teams. The participating hospital services, in the post-intervention phase of the study, will adopt these practice modifications for all new patients. It is important to note that the intervention does not involve a drug, technology, device, or any other intervention that directly reaches the patient, and poses no risk to the patients. Consequently, the need for informed consent has been waived by the IRB, and all eligible patients will be automatically included.

4.3. *Data collection : variables and measurements*

4.3.1. *Study procedures and execution*

4.3.2. *Intervention or exposure variable*

4.3.2.1. *Allocation of interventions and blinding*
Not applicable.

4.3.2.2. *Interventions or exposures – Other study designs*
The head and neck cancer team at the CHUM plans to implement the use of a new organisational system, independent of this study. This care coordination and organizational navigation system is aimed at optimizing the therapeutic trajectory for patients with head and neck cancers. This system facilitates collaboration within the multidisciplinary team by extracting relevant data from institutional computer systems (OACIS, PACS, MOSAIC, etc.), stratifying patients based on risk of receiving adjuvant treatment after surgery and sending various members of the multidisciplinary team automated reminders and target dates to complete specific tasks. It is important to note that this system affects members of the

multidisciplinary team in that it aims to improve coordination but does not directly impact patients or patient care. Norms of care and treatment modalities for patients remain the same.

Specifically, at time of booking operating room request, each patient is inserted in clinical calculator, which calculates a risk of requiring adjuvant therapy following surgery using our predictive model[12] that stratifies patients into low (normal-track) and high (fast-track) risk.

For high-risk patients (fast-track):

- Pre-operative radiation oncology consult done at same time as otolaryngology consult.
- Pre-operative dental consult.
    - If not done (or scheduled) 1 week prior to date of surgery, reminder email sent to dentist, radiation oncologist and surgeon.
- Pre-operative medical oncology consult request if any of the following are present:
    - clinical or imaging ENE (matted nodes, invasion of adjacent structures, clinically bulky/fixed nodes)
    - invasion of extrinsic muscle of tongue
    - bony invasion
    - involvement of pterygoid space
    - > 4 cm tumor
- Target date for post-operative pathology report set to 14 days post-operatively.
    - On day of surgery, a reminder email is sent to pathology department coordinator, pathologist, radiation oncologist and surgeon.
    - 5 days before target, a reminder email is sent to pathology department coordinator, pathologist, radiation oncologist and surgeon.
- When pathology report is out, surgeon and radiation oncology are automatically emailed to notify of new result.
- Target date for dental extraction set to 14 days after post-operative pathology report.

For low-risk patients (normal track):

- Pre-operative radiation oncology consult done at same time as otolaryngology consult.
- Target date for post-operative pathology report set to 28 days.
    - On day of surgery, a reminder email is sent to pathology department coordinator, pathologist, radiation oncologist and surgeon.
    - 5 days before target, a reminder email is sent to pathology department coordinator, pathologist, radiation oncologist and surgeon.
- When pathology report is out, surgeon and radiation oncology are automatically emailed to notify of new result.
- Target date for dental extraction set to 7 days after post-operative pathology report.

4.3.3. *Outcome variable*

- Surgery to post-operative radiation therapy (SPORT - defined as number of days from surgery to initiation of radiation therapy or chemoradiation) ≤42 days.
- Overall survival, with events defined as death from any cause.
- Locoregional survival, with events defined as locoregional recurrence (primary site or cervical node) or death.
- Distant metastasis-free survival, with events defined as distant metastasis or death.

- Recurrence-Free Survival, with events defined as any recurrence (local, regional, or distant). Deaths without recurrence are censored.
- Disease-free survival, with events defined as recurrence (any site) or death.

All oncologic outcomes are defined from date to surgery to date of event.

4.3.4. *Clinical and demographic variables*Patient demographics

- Age
- Sex
- Smoking status (current, previous, never)
- Number of pack-years
- Marijuana status (current, previous, never)
- Alcohol status (current, previous, never)
- Number of alcohol consumptions per week

- Prior medical conditions and active comorbidities
  - Prior head & neck malignancy (yes/no)
  - Prior non-head & neck malignancy (yes/no)
  - Prior head & neck radiation (yes/no)
    - If yes, dose (in Gray)
  - Charlson-Deyo Comorbidity index
  - ECOG score

4.3.5. *Covariates*Pre-operative tumour characteristics

- Tumour size on CT scan
- Tumour site (oral cavity vs larynx)
- Tumour subsite
  - Oral cavity: lip, alveolar ridge (maxillary or mandibular), hard palate, oral tongue, floor of the mouth, retromolar trigone, buccal mucosa
- Clinical T status
- Clinical N status
- Clinical M status

- Surgical and post-operative characteristics
  - Surgery duration (in minutes)
  - Surgical complication (yes/no)
  - Tracheostomy (yes/no)
  - Free flap (yes/no)
  - Local flap (yes/no)
  - Neck dissection (yes/no)
  - Post-operative hospital length of stay (in days)
- Pathological tumour characteristics
  - Tumour size
  - pT status
  - pN status
  - number of positive nodes
  - margin status
  - margin (in mm)
  - extranodal extension
  - perineural invasion

4.3.6. *Study conduct and specific strategies for minimizing biases*Some may argue that there are seasonal differences in treatment delays (ie. some periods during the year are more susceptible to causing in health care administration delays – for example, during holiday periods). In order to minimize this bias, we will run both control and intervention group for 12 months and 12 months, respectively.

4.4. *Statistical aspectsSample size*

The estimated sample size was calculated for our study. Employing a two-sided alpha of 0.05 and a beta of 0.20, we aim to investigate the impact of an intervention on the risk of prolonged S-PORT (>42 days). Based on prior Canadian literature, approximately 80% of patients have prolonged S-PORT [3,19,20]. Our hypothesis posits that with the intervention, the risk of prolonged S-PORT will decrease substantially to at least 50 percent. Based on sample size calculations, it has been determined that a cohort of 38 patients in each group will be necessary to detect statistically significant differences.

4.4.2. *Statistical analysis*

Statistical analysis will be performed using R statistical software. The aim of this pilot study of a new coordination intervention is to determine if the implementation of this intervention will result in higher adherence to recommended treatment delays (S-PORT ≤42 days). Descriptive characteristics will be presented as mean (standard deviation) or median (interquartile range) for continuous parameters and frequency distributions (number and proportion) for categorical parameters for all patient demographics and baseline characteristics. Univariate logistic regression will be used identify covariates associated with prolonged treatment time intervals. Multivariate logistic regression will be used to explore the independent association between this intervention and treatment time intervals. We will use a combination of the univariate logistic regression (with variables showing a noteworthy statistical association as indicated by a $P < 0.10$), expert opinions and variables that have been shown to be associated with treatment delays in the previously published literature to select covariates that are entered in the multivariate model. An alpha level of $P < 0.05$ was used as the cut-off for statistical significance in the multivariable analysis.

5. *Surveillance and safety*Not applicable.

6. *Ethical considerations*This study will comply with all applicable laws, regulations, and guidance regarding patient protection including patient privacy. As this study aims to evaluate the implementation of an administrative intervention that aims to improve care coordination between healthcare providers but does not directly reach patients, the study presents no risk to the patients. It is therefore proposed that the need for consent be waived. Participant information will be deidentified. Data will be collected and stored using REDCAP. A backup of the data will be stored on a USB key, kept in a secure locked room, until the project is completed. Only identified members of the research team will have access to the database for data management and conduction of the analyses. The data will be destroyed once the project is completed and the data has been analyzed (<7 years).

It is the intent of the collaborators to publish the study results. Results will be sent out to and disseminated at scientific meetings. Further, a manuscript will be prepared and if possible, published in a renowned scientific journal. No patient will be identifiable in the presentations or publications. All authors should meet the criteria for authorship, and all people who meet the criteria should be authors. Potential conflicts of interest should be disclosed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

1. Chen MM, Harris JP, Orosco RK, Sirjani D, Hara W, Divi V. Association of Time between Surgery and Adjuvant Therapy with Survival in Oral Cavity Cancer. *Otolaryngol Head Neck Surg*. Jun 2018;158(6):1051-1056. doi:10.1177/0194599817751679
2. Cheraghlou S, Kuo P, Judson BL. Treatment delay and facility case volume are associated with survival in early-stage glottic cancer. *Laryngoscope*. Mar 2017;127(3):616-622. doi:10.1002/lary.26259
3. Dayan GS, Bahig H, Johnson-Obaseki S, et al. Oncologic Significance of Therapeutic Delays in Patients With Oral Cavity Cancer. *JAMA Otolaryngol Head Neck Surg*. Jul 9 2023;doi:10.1001/jamaoto.2023.1936
4. Divi V, Graboyes EM. American College of Surgeons (ACS)/Commission on Cancer (CoC) – Approved Quality Metric for Head and Neck Cancer. https://www.ahns.info/acs-coc-hnc/
5. Fujiwara RJ, Judson BL, Yarbrough WG, Husain Z, Mehra S. Treatment delays in oral cavity squamous cell carcinoma and association with survival. *Head Neck*. Apr 2017;39(4):639-646. doi:10.1002/hed.24608
6. Graboyes EM, Garrett-Mayer E, Ellis MA, et al. Effect of time to initiation of postoperative radiation therapy on survival in surgically managed head and neck cancer. *Cancer*. Dec 15 2017;123(24):4841-4850. doi:10.1002/cncr.30939
7. Graboyes EM, Kompelli AR, Neskey DM, et al. Association of Treatment Delays With Survival for Patients With Head and Neck Cancer: A Systematic Review. *JAMA Otolaryngol Head Neck Surg*. Feb 1 2019;145(2):166-177. doi:10.1001/jamaoto.2018.2716
8. Hanna TP, King WD, Thibodeau S, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. *Bmj*. Nov 4 2020;371:m4087. doi:10.1136/bmj.m4087
9. Ho AS, Kim S, Tighiouart M, et al. Quantitative survival impact of composite treatment delays in head and neck cancer. *Cancer*. Aug 1 2018;124(15):3154-3162. doi:10.1002/cncr.31533
10. Shaikh T, Handorf EA, Murphy CT, Mehra R, Ridge JA, Galloway TJ. The Impact of Radiation Treatment Time on Survival in Patients With Head and Neck Cancer. *Int J Radiat Oncol Biol Phys*. Dec 1 2016;96(5):967-975. doi:10.1016/j.ijrobp.2016.08.046
11. Dayan G, Bahig H, Fortin B, et al. Predictors of prolonged treatment time intervals in oral cavity cancer. *Oral Oncol*. Nov 8 2023;147:106622. doi:10.1016/j.oraloncology.2023.106622
12. Dayan GS, Bahig H, Colivas J, et al. Preoperative Clinical and Tumor Factors Associated With Adjuvant Therapy for Oral Cavity Cancer. *JAMA Otolaryngol Head Neck Surg*. May 1 2025;151(5):466-475. doi:10.1001/jamaoto.2024.5250
13. NCCN Guidelines. Head and Neck Cancers. *NCCN Clinical Practice Guidelines in Oncology*. 2021;(Version 1.2021)
14. Duckett KA, Kassir MF, Nguyen SA, et al. Delays Starting Postoperative Radiotherapy Among Head and Neck Cancer Patients: A Systematic Review and Meta-analysis. *Otolaryngol Head Neck Surg*. Sep 20 2023;doi:10.1002/ohn.538
15. Graboyes EM, Halbert CH, Li H, et al. Barriers to the Delivery of Timely, Guideline-Adherent Adjuvant Therapy Among Patients With Head and Neck Cancer. *JCO Oncol Pract*. Dec 2020;16(12):e1417-e1432. doi:10.1200/op.20.00271
16. Sykes KJ, Morrow E, Smith JB, et al. What is the hold up?-Mixed-methods analysis of postoperative radiotherapy delay in head and neck cancer. *Head Neck*. Oct 2020;42(10):2948-2957. doi:10.1002/hed.26355
17. Divi V, Chen MM, Hara W, et al. Reducing the Time from Surgery to Adjuvant Radiation Therapy: An Institutional Quality Improvement Project. *Otolaryngol Head Neck Surg*. Jul 2018;159(1):158-165. doi:10.1177/0194599818768254
18. Graboyes EM, Sterba KR, Li H, et al. Development and Evaluation of a Navigation-Based, Multilevel Intervention to Improve the Delivery of Timely, Guideline-Adherent Adjuvant Therapy for

Patients With Head and Neck Cancer. *JCO Oncol Pract*. Oct 2021;17(10):e1512-e1523. doi:10.1200/op.20.00943
19. Graboyes EM, Garrett-Mayer E, Sharma AK, Lentsch EJ, Day TA. Adherence to National Comprehensive Cancer Network guidelines for time to initiation of postoperative radiation therapy for patients with head and neck cancer. *Cancer*. Jul 15 2017;123(14):2651-2660. doi:10.1002/cncr.30651
20. Murphy CT, Galloway TJ, Handorf EA, Wang L, Mehra R, Flieder DB, Ridge JA. Increasing time to treatment initiation for head and neck cancer: an analysis of the National Cancer Database. *Cancer*. Apr 15 2015;121(8):1204-13. doi:10.1002/cncr.29191

8. Annexes