UNIVERSITY OF CALGARY | Program for Undergraduate Research Experience (PURE)

FINAL REPORT AND REFLECTION

"*ADAPTIVE RADIATION THERAPY IN HEAD AND NECK CANCER*"

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INTRODUCTION

Head and neck cancer is the sixth most common malignancy worldwide with 350 000 deaths reported annually (1). Radiotherapy is one of the most common treatment modalities for head and neck cancer patients. Although head and neck cancer (HNC) survival is steadily increasing, the close proximity of tumor volumes to organs at risk (OARs) makes radiotherapy planning and delivery challenging for these patients. The design of radiotherapy treatment plans is based on CT images of patients acquired prior to the start of radiotherapy. However, changes may occur in patient setup and anatomy over the 6-7 weeks of daily radiotherapy treatment as a result of treatment side effects (e.g., dry-mouth and swallowing toxicities) leading to patient weight loss and tumour regression. This can result in the delivery of radiotherapy doses to the patient that deviate from the highly precise planned dose. Dose differences can result in over dosage of organs at risk, resulting in radiation-induced complications that may significantly affect one's quality of life (QoL) (2). Conversely, under dosages to tumor volumes may increase the risk of cancer recurrence.

Xerostomia (dry mouth) and dysphagia (swallowing problems) are both the main acute and late complications adversely impacting QoL during and after radiotherapy (3). Xerostomia is the most common complication for patients undergoing radiation therapy as a result of damage to the salivary glands (3). Current literature has identified that limiting the volume of the parotid glands and submandibular glands receiving a high radiation dose is as a major factor in reducing the severity of xerostomia. However, the close proximity of these glands to tumour volumes and lymph nodes indicates a potential risk of reducing radiation dosages to these glands without impeding local regional tumour control. Similarly, dysphagia is associated with high radiation dosages to the critical structures necessary for swallowing such as the pharyngeal and laryngeal muscles, which are also found in close proximity to tumours (3).

Adaptive radiation therapy (ART) is a leading topic of research in radiation oncology that monitors for daily tumour and normal tissue dose variations by using online surrogate measures (i.e., weight loss) and/or resource-intensive offline dose recalculations. Preliminary studies suggest that ART interventions may lead to improvements in clinical outcomes and post-treatment quality of life without compromising tumour control (4). As a result, artificial intelligence-based approaches can improve prediction and monitoring of radiotherapy-induced side effects through identification of systematic changes. However, implementation of ART is challenging given the lack of clear guidelines on rescanning/re-planning timing, the high resource requirement for treatment re-planning, and the need for an increasing amount of data to be analyzed to ensure process quality. Formal ART clinical trial design continues to be hampered by open questions regarding the identification of re-planning candidates and timing. It is unlikely that every patient will benefit from ART, and strategic selection of patients who may benefit from ART focuses on the identification of selection criteria based on pre-treatment characteristics, initial plan parameters, during treatment anatomical changes, and by selection during treatment based on dosage changes (2).

The goal of ART-related research is ultimately to identify precise criteria regarding which HNC patients would benefit from re-planned treatment and at what time during the treatment course. By gaining insight into previously undiscovered patterns in the head and neck patient cohort, this work has the potential to further improve the quality of care offered to cancer patients. We hypothesize it will not only further reduce the incidence of treatment-related toxicities and improve post-treatment quality of life of patients with cancer but also improve the allocation of essential clinical resources.

METHODS

My summer research project was split into two related projects to accommodate ethics approval processes: “Anatomical changes” and “Quality of Life.” For the QoL project, ethics approval was required as a result of this project being clinic-based and revolving around patient interaction. The anatomical changes project was initiated in the meantime.

Anatomical Changes

ART-related research requires extensive processing of the patient records and analysis of cohort-wide clinical outcomes and toxicity data to develop models capable of accurately predicting any mid-course changes in plan quality. This project involved the analysis of anatomical changes in patients occurring during the course of radiation therapy and compilation of pre-treatment characteristics prior to radiation therapy.

Collaboration between the Divisions of Radiation Oncology and Medical Physics at the Tom Baker Cancer Centre has established a retrospective cohort of 250 patients with advanced stage head and neck cancer (treated November 2015 – September 2018). Data collection of pre-treatment characteristics utilized the ARIA-MO system to compile a database of disease laterality, stage at diagnosis, treatment type, radiation dosage and fractions, treatment date, p16 status, EBV status, alcohol and smoking intake, age at diagnosis, gender, chemotherapy agent, Charlson comorbidity score, ECOG, height, initial and final BMI and weight.

Data collection of anatomical changes utilized the ARIA-RO system to compare planned radiation doses to estimated delivered doses using on-unit cone beam CT (CBCT) images for a cohort of 250 patients. Calculated anatomical changes included changes in patient face diameter, neck diameter, chin position, head rotation and shoulder position variations, which current literature has identified as potential surrogate measures of radiation dose changes. Change in face diameter was calculated using the axial plane to find the maximum difference in lateral face diameter between the inferior alveolar process and the superior mandible body. Change in neck diameter was calculated using the axial plane to find the maximum difference in lateral neck diameter anterior to the spinal vertebrae, inferior of the hyoid. Change in chin position was calculated using the sagittal plane to determine the difference in position of the mental protuberance at the spinous process (midline). Weight loss about the neck and shoulders was calculated using the coronal plane to find the maximum difference below ear lobes of both the right and left sides posterior of the acromioclavicular (AC) joint. Change in shoulder position was calculated using the difference in AC joint on both the axial and coronal planes for both right and left shoulders. These measures were used to calculate an overall shoulder position change using the Pythagoras theorem ($a^2+b^2=c^2$), where the axial and coronal calculations represent a and b. Head rotation was calculated using the axial plane to determine the difference in position of the anterior ramus inferio-posterior of C.1 vertebral foramen (Figure 1). Twelve anatomical change measures were measured and calculated using the CBCT images.

The radiation dosages received by OARs and tumour volumes was obtained from prior data collection to calculate dosimetric changes in these areas of interest. OARs of interest in this analysis included the brainstem, ipsilateral and contralateral parotid glands, ipsilateral and contralateral submandibular glands, pharyngeal constrictor muscles, and the spinal cord. Tumour volumes included the main tumour volume (CTV7000 at D2% and D95%) and prophylactic nodal coverage for suspected microscopic spread (CTV5940 at D20% and D95%), where DXX% indicates the maximum dose received by an XX% of the structure. Varying D% indicated regions that received differing percentage of radiation dosages. Three additional pre-treatment characteristics that were collected previously were also included in the data set for analysis (Age, Initial BMI and Change in BMI). The final dataset for analysis included 12 calculated anatomical changes, 3 pre-treatment characteristics, 11 initial radiation dosages to OARS and tumour volumes, and 11 dosimetric changes to OARS and tumour volumes for a total of 37 variables.

Conventional correlation analysis and hierarchical clustering were performed to assess group-wise correlations between the anatomical changes, pre-treatment characteristics and dosimetric changes to OARs and tumour volumes. K-medoid clustering and principal components analysis (PCA) were conducted to stratify patients according to potentially correctable weight loss/shrinkage effects vs. daily on-unit setup variability; clustering was conducted using anatomical change and dosimetric change measures. Mann-Whitney U-test with Bonferroni correction determined p-values as p/n, where n= 37, and provided a conservative analysis to determine statistical significance between the two clusters by lowering the significance value by accounting for the number of variables in the dataset. However, this post-hoc test suffers from a loss of power since it overcorrects for type I errors (false positives) and can be too strict in some fields. This can result in significant differences being deemed non-significant due to an increased number of type II errors (false negatives). The Benjamin Hochberg post-hoc test was also run to control for a lower proportion of false positives to combat the limitations of the Bonferroni test and for a more robust statistical analysis. All analyses were run utilizing R studio.

Quality of Life

Although clinician evaluation provides invaluable information on treatment-related effects, studies have shown that patients may rate their dysphagia and xerostomia more severely than clinicians and the true impact of these side effects may be underestimated (5). This project assessed the impact of anatomical changes and dose deviations on post-treatment quality of life measures. A questionnaire package for patients was designed using questionnaires validated by literature. The package included a consent form and three self-administered questionnaires (MDASI, MDADI, and XQ) to determine patient-reported outcomes (Figure 2). The M.D. Anderson Symptom Inventory (MDASI) questionnaire was used to evaluate overall QoL of patients (6). The M.D. Anderson Dysphagia Inventory (MDADI) was used to evaluate the impact of dysphagia on the QoL of patients (7). The xerostomia-specific questionnaire (XQ) was used to evaluate patient-reported xerostomia (8).

Data collection was initiated in mid-June. HNC patients returning for follow-ups were given the questionnaires to fill out whilst waiting for their appointments. Administration of questionnaires was coordinated with head nurses to ensure that clinical efficiency was not impacted; data was collected weekly. Data collection is still in progress and is estimated to be completed by the end of September. Analysis will be conducted shortly after all data has been collected during the year.

For analysis, estimated delivered doses as calculated using deformable image registration workflows will be aggregated with the QoL data. Conventional statistical analysis will assess correlations between planned doses, QoL measures, pre-treatment characteristics, and delivered doses. Dose-volume histograms of patients will also be compared with QoL scores. This project strives to further identify parameters that will effectively select patients who are expected to benefit most from ART in terms of expected effect on post-treatment quality of life. Artificial intelligence methods have significant promise in this domain, with capabilities to identify complex patterns and associations in patient data, with potential for future adoption at the Tom Baker Cancer Centre.

RESULTS

Anatomical Changes

Correlation plot: There is a positive correlation between increased dosages to the spinal cord and the pharyngeal constrictors and weight loss in the neck/shoulder region and changes in BMI and face and neck diameter (Figure 3).

Principle Components Analysis and Clustering: The clustering assigned 76 patients to cluster 1, which is hypothesized to exhibit systematic changes and 174 patients to cluster 2, indicated as exhibiting random changes. These results indicated that 30.4% of the cohort exhibited systematic anatomical changes. The PCA indicates various correlations between anatomical and dosimetric measures (Figure 4). For dimension 1 (x-axis), change in BMI and face and neck diameter are correlated with dosimetric changes to the spinal cord, pharyngeal constrictors, tumour volume (CTV7000 D2%) and areas surrounding the tumour (CTV5940 D20%). For dimension 2 (y-axis), changes in head rotation/shift and chin position are correlated with dosimetric changes to the tumour volume (CTV7000 D95%) and areas surrounding the tumour (CTV5940 D95%).

Statistical analysis: Mann-Whitney U tests with Bonferroni post-hoc tests indicated there were statistically significant differences between the clusters for all of the anatomical measures except head rotation and all of the pre-treatment characteristics except age ($p<0.05$). Radiation dosages were statistically significant between the clusters for only ipsilateral submandibular glands ($p<0.05$). There was a statistically significant difference for all dosimetric changes except areas surrounding the tumour (D95%) and both ipsilateral and contralateral parotid glands ($p<0.05$). Benjamini-Hochberg correction and MANOVA did not reveal additional relevant statistically significant differences, supporting the Mann-Whitney U tests.

Quality of Life

Data collection is still in progress for this project, the analysis is yet to be run. Currently, 141 questionnaires have been collected from 10 days of clinic attendance from patients of up to six different physicians.

DISCUSSION/ CONCLUSION

The results indicate that a positive correlation between increased dosages to central-axis anatomical structures (spinal cord, pharyngeal constrictor) and systematic weight-loss effects (change in BMI and weight loss through the face and neck). In line with current literature, clustering indicated that 30.4% of the cohort exhibited systematic anatomical changes, potentially correctable by re-planning. Overall, the results indicate that on-unit CT measures regarding systematic weight loss about the neck and shoulders and change in BMI can identify patients that will benefit from ART re-planning for valuable reducing in xerostomia and dysphagia outcomes. These changes in patient anatomy may be causing a higher radiation dosage to the tumour volume, but subsequently resulting in higher dosages to the salivary glands. Although this results in a higher tumour volume coverage, this may also result in higher toxicities in patients and significantly impede patient QoL post-radiotherapy treatment. In contrast, loss in tumour volume coverage may be due to random effects such as change in chin position and head rotation that can be further improved through modifications of mobilization techniques to reduce setup uncertainties throughout the course of radiotherapy.

Currently, ART candidates are identified by a change in body contour exceeding 1.5 cm for a physician consult. Application of various supervised and unsupervised learning paradigms to the studied anatomical changes can lead to cohort-wide insight that can effectively select patients who are expected to benefit most from plan adaptation during treatment for further development of personalized treatment. On-unit CT measures appear to be able to distinguish random and systematic dosimetric effects, correlated with changes in dose as expected. As a result, these measures can be utilized to improve artificial intelligence-based patient monitoring and intervention techniques.

Both projects initiated over the summer will be continued during the fall and winter semesters for further development of ART.

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LEARNING & SKILLS DEVELOPMENT

During this summer research, I have had the opportunity to develop both my teamwork and fundamental skills. Through the anatomical changes study, I learned the necessity of being able to adapt to unexpected situations. With an initial plan to spend the first three months collecting data for a quality of life-based data and the last month writing a manuscript, this plan evolved due to ethics approval timelines. In the meantime, I decided to start a separate smaller project in order to be efficient with time. By the time of ethics approval for the QoL project, the smaller project that was initiated had enough of a base to run initial analyses and the abstract was accepted for the CASCH conference at the University of Alberta. This project also gave me the opportunity to learn the patience required for data collection, in addition to the trial-and-error required to run statistical analyses correctly. The anatomical changes project was not planned, but it established a foundation for many of the analyses I will have to run in the future for continuation of the quality of life project. Additionally, the analyses skills I learnt will be a formidable asset for my final year in the Bachelor of Health Sciences for my thesis. I will be continuing research work with my supervisor throughout the year through an independent research class (MDSC 528). The results of this project will also be contributing to a larger study being conducted by a medical physics PhD of the Tom Baker Cancer Centre candidate on developing supervised and unsupervised "artificial intelligence" models of ART, and I will be working on this further throughout the year.

Working on the quality of life project played a huge role in developing my interpersonal and teamwork skills. The most important aspect of data collection for this project was to maintain clinical efficiency such that patients are not waiting longer for their follow-up appointments, but still had enough time to fill out the questionnaires. As a result, there was constant coordination occurring with the radiation oncologists and the nurses managing the HNC clinics to ensure that my study was not disrupting clinical flow. Additionally, it was extremely important to respect the wishes of patients and to present the questionnaires in a manner that was not forceful. The skills I learned from this project will be instrumental to interactions with patients as a researcher, in addition to strengthen general communication and interpersonal skills. Continuation of this project through the MDSC 528 class will further develop my manuscript writing skills, with the goal of obtaining a publication in a refereed journal from this project.

Overall, my research experience through PURE was multifaceted, leading to the development of a multitude of skills encompassing writing, presentation, communication, teamwork, and interpersonal skills. I would like to thank the PURE awards committee for funding me to undergo this research experience. I would also like to thank Dr. Harvey Quon and Sarah Weppler for their constant guidance throughout this summer, as well as continued guidance in the future. They played a central role in developing a summer research project through which I was able to develop a wide variety of skills that will be instrumental in both future studies and endeavours.