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Observational study of volume effects of salivary glands under radio(chemo)therapy of head and neck tumors

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Zusammenfassung

Zielsetzung

Tumoren von Kopf und Hals sind weit verbreitete Krebsarten in Deutschland mit etwa 17.000 Neuerkrankungen jährlich.[1] Durch die anatomischen Gegebenheiten und der relativ hohen Strahlenempfindlichkeit dieser Tumoren sind Radiotherapie bzw. Radiochemotherapie die Therapie der Wahl.[2–4]

In den letzten zwei Jahrzehnten wurden einige Arbeiten zur Charakterisierung von anatomischen Veränderungen von Speicheldrüsen und den resultierenden Toxizitäten unter Radiotherapie veröffentlicht.[5–18]

Auch Übersichtsarbeiten der letzten Jahre bestätigen Volumenveränderungen, speziell Verkleinerungen, von Speicheldrüsen sowie einen vermuteten Zusammenhang von Mundtrockenheit (Xerostomie) mit veränderten Volumina und der Zusammensetzung des Speichels unter Radiotherapie.[9, 17–19]

Die Zielsetzung dieser Arbeit war die Identifikation und eine Quantifizierung von Effekten der Radiotherapie auf Speicheldrüsen, speziell ihrer Volumina und die Toxizitäten, um so die Lebensqualität von Patientinnen und Patienten mit Kopf-Hals-Tumoren langfristig zu verbessern.

Material & Methoden

Wir identifizierten 269 Patientinnen und Patienten, die unsere initialen Einschlußkriterien erfüllten. Von diesen 269 wurden 225 wegen den im Abschnitt 4.1 detailliert beschriebenen Kriterien (unter anderem Überlebenszeit, palliative Situation, CUP-Syndrom etc.) von der weiteren Auswertung ausgeschlossen. In der endgültigen Probandengruppe befanden sich 44 Personen mit Tumoren von Kopf und

Hals, die zwischen 2011 und 2015 am Uniklinikum Regensburg Radiotherapie erhielten.

Dosisebenen (D5 bis D95) und mittlere Dosis wurden für je beide Parotiden sowie beide Glandulae submandibulares aus den Dosis-Volumen-Histogrammen (DVH's) bestimmt. Die Toxizitäten (Xerostomie und Dysphagie) sowie die Volumina der Speicheldrüsen wurden vor der Therapie, nach dem Ende der Bestrahlung, sowie nach drei, sechs, und zwölf Monaten und zusätzlich variabel zu Zeitpunkten bis zu 36 Monaten[1] nach dem Ende der Bestrahlung gemessen.

Unsere gesammelten Daten wurden mit Hilfe von Python[20], Pandas[21] und R[22] aufbereitet und analysiert.

Ergebnisse

Die endgültige Patientengruppe bestand aus 44 Personen im Alter zwischen 48 und 77 Jahren mit 41 männlichen Patienten sowie drei weiblichen Patientinnen. Dreizehn Personen wurden mit Radiotherapie (RT) alleine behandelt, 31 erhielten sowohl Radio- als auch zusätzlich Chemotherapie (RCT).[2]

Die Volumina der Speicheldrüsen verkleinerten sich im Durchschnitt um 34% (Parotiden) sowie 18% (Submandibulares) im Vergleich zwischen vor und nach dem Ende der Therapie.[3] Weder die Volumina der Parotiden noch die der Submandibulares erholten sich innerhalb von 36 Monaten nach Ende der Therapie.[4]

Es gab keinen nachweisbaren Unterschied zwischen den beiden Behandlungsgruppen (RT versus RCT)[5] und ebenfalls keinen Unterschied in unseren Gruppen der Lokalisationen der Tumoren[6] im Bezug zur Volumenänderung.[7]

[1] Da Nachsorgetermine mit Bildgebung variabel terminiert und in der Regel innerhalb von Zeitfenstern stattfanden, waren die Zeitpunkte teilweise sehr breit gestreut. Eine detaillierte Beschreibung unserer zeitlichen Auswertung findet sich in Abschnitt 3.7.2.

[2] Details in Abschnitt 4.2.

[3] Details in den Abschnitten 4.4 und 4.5.

[4] Details in Abschnitt 4.6.

[5] Details in Abschnitt 4.10.

[6] Details zu diesen verschiedenen Lokationsgruppen finden sich in Abschnitt 3.7.1.

[7] Details in Abschnitt 4.9.

Wir konnten eine schwache Korrelation zwischen der Volumenänderung und der mittleren Dosis nachweisen.[8] Eine Lokationsgruppe (Tumoren der Nasopharynx, *NAS*) erhielten signifikant weniger Dosis als alle anderen Gruppen ($p < 0.01$).[9]

Xerostomie nach Ende der Therapie unterscheidet sich nicht signifikant von der Xerostomie vor Beginn der Therapie ($p = 0.08$). Die Xerostomie an den Zeitpunkten drei, sechs, und zwölf Monate nach Ende der Therapie sind signifikant höher als vor Therapiebeginn ($p < 0.001$ für alle diese Zeitpunkte).[10]

Dysphagie nach Ende der Therapie unterscheidet sich signifikant von der vor Therapiebeginn ($p < 0.001$). Dysphagie an den Zeitpunkten drei, sechs, und zwölf Monate nach Ende der Therapie sind ebenfalls signifikant höher als vor Therapiebeginn ($p < 0.001$ für alle diese Zeitpunkte). Die Dysphagie zu diesen Zeitpunkten unterscheidet sich nicht signifikant von der nach Therapieende ($p > 0.05$ für alle), worin sich zeigt, daß es hier wohl ebenfalls keine Erholung nach Therapieende gibt.[11]

Wir fanden signifikante Unterschiede der Dysphagie zwischen den Lokationsgruppen der *NAS* Gruppe (12 Monate, $p < 0.01$) sowie der *MULTI* Gruppe (3 Monate, $p < 0.01$). Es gab keine Xerostomie vor Therapiebeginn in keiner der Lokationsgruppen. In den *LAR* und *ORO* (Tumoren des Oropharynx) entwickelte sich Xerostomie früher als in den restlichen Gruppen (ungefähr drei Monate nach Therapieende). Dysphagie war teilweise bereits vor der Therapie existent, mit Ausnahme der *MUN* und *ORO* Gruppen. Die *MULTI* Gruppe zeigte die stärkste Zunahme von Dysphagie innerhalb der ersten drei Monate nach Therapieende, mit Rückgang danach. Die Dysphagie war am stärksten 3–6 Monate nach Therapieende und danach in allen Gruppen rückläufig.[12]

Wir konnten keinen signifikanten Zusammenhang zwischen Xerostomie und Drüsenvolumen zeigen. Ebenso konnten wir keinen signifikanten Zusammenhang zwischen Dysphagie und Drüsenvolumen zeigen.[13]

Beginnend etwa drei Monate nach Therapieende zeigte sich ein deutlicher Zusammenhang von Xerostomie und der mittleren Dosis, die die Drüsen erhalten hatten: Je größer die Dosis, desto höher der Grad der Xerostomie. Wir konnten

[8] Details in Abschnitt 4.7.
[9] Details in Abschnitt 4.8.
[10] Details in Abschnitt 4.11.1.
[11] Details in Abschnitt 4.11.2.
[12] Details in Abschnitt 4.12.
[13] Details in Abschnitt 4.14.

andererseits keinen signifikanten Zusammenhang zwischen der erhaltenen Dosis der Submandibulares mit dem berichteten Grad der Xerostomie finden.[14]

Diskussion

Die prominenteste Limitation dieser Arbeit ist wohl die Größe der endgültigen Probandengruppe von nur $N = 44$ Personen mit vollständigen Datensätzen. Da wir aber mit $N = 269$ Personen begonnen haben (Details zur Auswahl im Abschnitt 4.1), scheinen wir trotz allem eine solide Datenbasis zu haben: Wir konnten nicht nur die in der Literatur beschriebenen Volumenänderungen der Speicheldrüsen nachvollziehen (Details im Abschnitt 4.5), sondern auch die spärliche Datenlage zu den Glandulae submandibulares verbessern.

Darüber hinaus konnten wir auch neue Daten zur Entwicklung von Toxizitäten und Volumenänderungen erheben: Wir können in dieser Arbeit auch über Zeitpunkte bis zu 36 Monate nach Therapieende berichten. Solche Berichtszeiträume sind in der einschlägigen Literatur selten.[15]

Als Resultat der von uns gezeigten signifikanten Volumenänderungen stellen sich uns schlußendlich zwei wichtige weiterführende Fragen:

- Gibt es aufgrund der Volumenänderungen signifikante Änderungen in der Geometrie anatomischer Gegebenheiten, insbesondere in der Lage der Speicheldrüsen in Bezug auf die ROI's (*regions of interest*)?
- Als Resultat dieser eventuellen Änderungen der anatomischen Gegebenheiten, gibt es die Möglichkeit bzw. gar eine Notwendigkeit, die Therapieplanung während der laufenden Bestrahlung, zwischen den fraktionierten Bestrahlungen, zu re-evaluieren, um die Nebenwirkungen und Toxizitäten der Therapie zu verringern?

Antworten auf diese beiden oben genannten Fragen könnten zu einer merklichen Verbesserung der Lebensqualität von Patientinnen und Patienten mit Tumoren von Hals und Kopf unter Strahlentherapie beitragen.

[14] Details in Abschnitt 4.15.
[15] Details in Section 2.2.4

Chapter 1

Abstract

1.1 Purpose

Head and neck tumors are common cancer in Germany that registers approximately 17.000 new cases annually.[1] Because of the anatomical location and relatively high radiosensitivity of the tumors, radiotherapy (RT) and radiochemotherapy (RCT) are the treatments of choice.[2–4]

In the last two decades, many efforts have been made to characterize anatomic changes of salivary glands and the resulting toxicities (especially xerostomia) after radiotherapy.[5–18]

Recent literature reviews confirmed that gland volumes are reduced after radiotherapy and xerostomia is linked to changes in volume and composition of salivary glands.[9, 17–19]

The purpose of this thesis was to determine the effects of radiotherapy on salivary glands, especially their volume and toxicities, in our patient collective to minimize toxicities and to improve quality of life in patients with head and neck tumors.

1.2 Materials and Methods

We identified 269 patients matching our inclusion criteria. From these, 225 patients were excluded as described in section 4.1. Finally 44 patients with head and neck cancer treated with radiotherapy between 2011 and 2015 participated in the study.

Dose levels (D5 to D95) and mean dose were determined for each parotid and submandibular gland from dose-volume histograms (DVHs). Toxicities (xerostomia and dysphagia) and gland volumes were measured before treatment and after 1, 3, 6, and 12+ months after the completion of the treatment.

The data was analyzed using Python[20], Pandas[21] and R[22].

1.3 Results

The final patient collective contained 44 patients between 48 and 77 years of age with 41 male and three female patients. Thirteen patients received radiotherapy (RT) only, 31 received both radio- and chemotherapy (RCT).[1]

Gland volumes decreased by an average of 34% (parotids) and 18% (submandibulars) after RT.[2] Volumes of neither parotids nor submandibular glands were recovering within the first 36 months after end of treatment.[3]

There was no difference between treatment (RT vs. RCT)[4] or tumor location groups[5] in gland volume decrease.[6]

A weak correlation was found between gland volume changes and mean gland doses.[7] One tumor location group (tumors of the nasopharynx, NAS) received significantly lower doses than the other groups ($p < 0.01$). [8]

Post-RT xerostomia is not significantly different from pre-RT xerostomia ($p = 0.08$). Xerostomia at three, six and twelve months after end of RT are each significantly higher than pre-RT ($p < 0.001$ each).[9]

Post-RT dysphagia is significantly different from pre-RT dysphagia ($p < 0.001$). Dysphagia at three, six and twelve months after end of RT are also significantly higher than pre-RT ($p < 0.001$ each). Dysphagia at three, six and twelve months

[1] Details in Section 4.2.
[2] Details in Sections 4.4 and 4.5.
[3] Details in Section4.6.
[4] Details in Section 4.10.
[5] For details on these tumor location groups and their abbreviations see section 3.7.1
[6] Details in Section 4.9.
[7] Details in Section 4.7.
[8] Details in Section 4.8.
[9] Details in Section 4.11.

after end of RT are not significantly different from dysphagia after RT ($p > 0.05$ each) indicating there is no recovery within this timeframe.[10]

We found significant differences between tumor location group dysphagia means for the NAS group (12 months, $p < 0.01$) and the MULTI group (3 months, $p < 0.01$). Xerostomia was not present before RT in either of the tumor location groups. In the LAR and ORO groups xerostomia was developed earlier (after RT) than in the other ones (after approximately three months). Except for the MUN and ORO groups, dysphagia was already present before RT. The MULTI group showed the largest increase in dysphagia within the first three months after end of RT and decreased afterwards. Dysphagia peaked at 3–6 months in all groups and decreased afterwards.[11]

No significant correlations between xerostomia and gland volume changes could be identified.[12] Also, no significant correlations between dysphagia and gland volume changes[13] or between toxicities and treatment (RT vs. RCT) could be identified.[14]

Starting at approximately three months after end of RT the grades of xerostomia are clearly associated with the received mean parotid gland dose - the more dose the parotids received, the higher the grade of xerostomia. There is no evidence for correlation of mean gland dose for the submandibular glands with neither xerostomia nor dysphagia.[15]

1.4 Discussion

A limiting factor for deductions from results in this thesis might be the relatively small number of patients with complete data sets ($N = 44$). As we started with $N = 269$ patients and carefully selected and documented our selection process (for details please see section 4.1) our basis looks solid: We not only could reproduce the changes in gland volume as described in literature (for details please see section 4.5) but also expand the data sets available for volume changes of the submandibular glands.

[10] Details in Section 4.11.
[11] Details in Section 4.12.
[12] Details in Section 4.14.
[13] Details in Section 4.14.
[14] Details in Section 4.13.
[15] Details in Section 4.15.

Although we only had complete data sets for $N = 44$ patients we could determine new information about the development of toxicities and volume changes: We found and reported data for up to 36 months after end of radiotherapy in this thesis, which has rarely been reported[16] so far.

There are two interesting questions arising as a conclusion of the changes in gland volume shown in this thesis:

- Are there significant changes in the anatomy with respect to the salivary glands with effects on the regions of interest?
- As a result of these eventual changes in anatomy, is there an option for re-planning during radiotherapy to further minimize the side effects and toxicities?

Answering these two questions could eventually lead to increase in the quality of life for patients with head and neck tumors treated with radio- or radiochemotherapy.

[16] Details in Section 2.2.4

Chapter 2

Introduction

SALIVARY GLANDS ARE PERHAPS MOST APPRECIATED BY THOSE WHO SUFFER THE LOSS OF THEIR SECRETORY FUNCTION.

– M.H. Aure, 2015 [23]

2.1 Background

Head and neck tumors are common cancer in Germany that registers approximately 17.000 new cases annually.[1] Because of the anatomical location and relatively high radiosensitivity of the tumors, RT and RCT are the treatments of choice.[2–4]

2.1.1 Head and Neck Tumors

Head and Neck Tumors (HNT) are malignant neoplasms of soft tissue origin that develop in the oral cavity including the lips, nasal cavity, paranasal sinuses, pharynx, larynx and salivary glands. Most head and neck cancers are Squamous Cell Carcinoma (SCC) and adenocarcinomas from associated secretory glands.[4] HNTs are strongly associated with environmental and lifestyle risk factors, particularly tobacco use, regular alcohol consumption, and certain viruses (especially Human papillomavirus (HPV) and Epstein-Barr virus (EBV)).[4]

These tumors can be further classified by their origin using the ICD-10 manual.[24] We particularly looked at tumors located at the oral cavity (lips, tongue, mouth,

gums and palate; C00-C06), tonsils and oropharynx (C09-C10), nasopharynx and pyriform sinus (C11-C12), hypopharynx (C13) and tumors of the larynx (C32).

At Regensburg University Clinic (UKR), head and neck tumors are commonly treated by intensity modulated radiotherapy (IMRT) and combined with chemotherapy (mostly Platins[1], Paclitaxel, Docetaxel, Fluorouracil, and Cetuximab) and surgery eventually, depending on the case. Total radiation doses to the primary tumor volume are 60–70 Gy applied in fractions of 1.8–2.2 Gy during 6–8 weeks of treatment.

2.1.2 Organs at Risk

Despite the advancements of radiotherapy techniques, radiation induced complications are frequently experienced in patients due to the inevitable irradiation of healthy tissue surrounding the target volume. In radiotherapy of head and neck tumors the most important organs at risk (OAR) are the salivary glands (especially the parotid glands (PG) and submandibular glands (SMG)) due to their anatomical proximity. [11–13, 16, 25]

In the last two decades, many efforts have been made to characterize anatomic changes of salivary glands and the resulting toxicities (especially xerostomia) after radiotherapy.[5–18]

2.1.3 Gland Doses, Salivary Function, and Toxicities

The mean salivary gland dose is correlated with salivary function.[26] A number of studies have proposed mean doses ranging between 20 and 30 Gy to the parotid gland.[27–29] Salivary function of the parotid gland gradually decreases with doses between 20 and 40 Gy, and a $>75\%$ decrease occurs over 40 Gy.[26, 28, 30] A mean dose of 36 Gy substantially reduces its function level, with further reduction occurring after completion of RT without recovery during the following 2 years.[26]

At the moment, mean doses of <26 Gy for each PG and <32 Gy for the SMG are recommended.[26]

[1] Cisplatin, Carboplatin, Oxaliplatin, and combinations

Apoptosis (and subsequent decrease in gland volume) is one of the mechanisms discussed to cause xerostomia[11, 31]. Xerostomia is also linked to changes in volume and composition of salivary glands.[9, 17–19]

Sparing at least one parotid or even one submandibular gland results in a decreased rate of xerostomia[26]; and xerostomia was "significantly decreased when the mean dose of at least one parotid gland was kept to <25.8 Gy with conventional fractionation."[28] Another study finds similar numbers and concludes that if a mean dose < 26 Gy for "at least one parotid gland can be achieved then this is sufficient to reach complete recovery of pre-RT salivary flow rates"[32].

2.2 Objectives

2.2.1 Overview

The objective of this thesis is to determine the effects of radiotherapy on salivary glands[2], especially their volume and toxicities, in our patient collective.

We focused on answering the following questions (details below):

A. Gland Volumes

- A.1 Are gland volumes different before and after radiotherapy?
- A.2 How big is the difference, if any?
- A.3 Are gland volumes recovering to their initial volume after radiotherapy within 12 (24, 36) months?
- A.4 Are gland volumes changes related to the doses received during radiotherapy?
- A.5 Are received doses different in each tumor location group?
- A.6 Are changes in gland volume different in each tumor location group?
- A.7 Are changes in gland volume different in treatment groups (RCT / RT)?

B. Toxicities

[2] Whenever we mention salivary glands we specifically address the parotid and submandibular glands throughout this thesis.

B.1 How are toxicities (xerostomia and dysphagia) developing after radiotherapy?

B.2 Are toxicities related to tumor location groups?

B.3 Are toxicities different in treatment groups?

B.4 Are toxicities related to gland volume changes?

B.5 Are toxicities related to received doses?

A brief overview about each question is given below. Details about methodology is provided in Chapter 3 (Material and Methods).

2.2.2 A.1: Are gland volumes different before and after radiotherapy?

The volume loss of salivary glands during and after radiotherapy is well documented in literature. [5, 12, 14, 16, 19, 33–53]

Most studies focus on the PG[5, 16, 17, 33, 34, 36–45, 47–50, 52, 53]. Studies including the SMG exist[12, 14, 35, 46, 48, 51, 53] but are less common.

Our first objective was to identify any volume changes in our patient collective. Results can be found in Section 4.4 (Objective A1: Gland volumes before and after RT).

2.2.3 A.2: How big is the difference, if any?

According to literature mean PG volume decreases from baseline (before start of treatment) to after end of RT between 17% and 38% (mean: 28%). [5, 33, 35–40, 42, 43, 45–51].

Mean SMG volume decreases are reported between 14% and 34% (mean: 23%) from baseline to after end of RT.[12, 14, 35, 46, 48, 51].

For this objective, we looked at volume decreases for each gland in our patient collective for comparison with previously published data. Results can be found in Section 4.5 (Objective A2: Quantification of gland volume changes).

2.2.4 A.3: Are gland volumes recovering to their initial volume after radiotherapy within 12 (24, 36) months?

Most publications about the recovery of salivary glands after radiotherapy focus on the parotid glands with salivary flow as their endpoint.[8, 28, 29, 32, 54–57]

Studies with focus on recovery and volume endpoints include data for time-frames from zero months (directly after end of radiotherapy) up to 30 months maximum.[12, 16, 52, 53] Only two of them includes data on the submandibular glands beyond the end of radiotherapy, at 24 months.[12, 53]

An overview of the published data about parotid gland volume development with time is shown in Fig. 2.1. None of the reported data shows complete recovery to pre-treatment gland volumes. At the end of the reporting timeframe (24 months, in one case 30 months) parotid gland volumes are either as small as right after the end of RT (-30%) [16] or 16% and 20% less than before RT, respectively [12, 52].

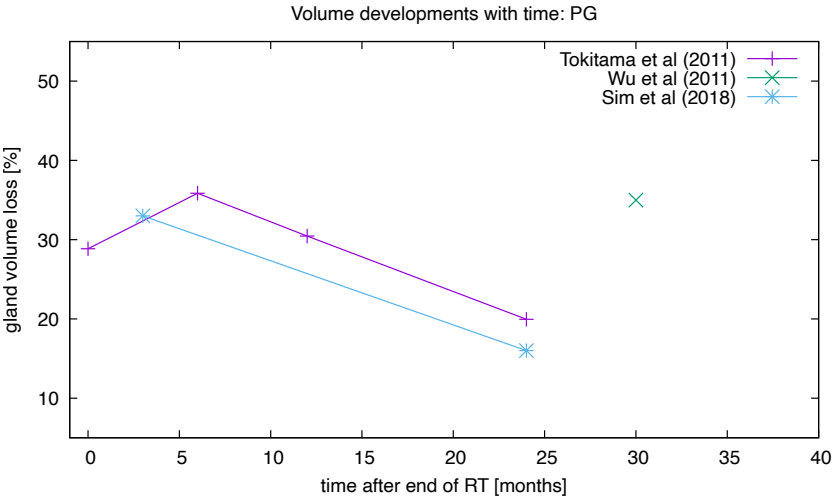


Figure 2.1: Comparison of published data of the development of parotid gland volume with time: Tokitama et al.[52], Wu et al.[16], and Sim et al.[12].

For the submandibular glands there is less published data: Sim et al.[12] report a submandibular gland volume loss after three months of 33% which even worsens with time (49% less than before treatment after 24 months). Uchiyama et al.[53] start with a loss of 14% and end with -17% after 24 months. An overview is shown in Fig. 2.2.

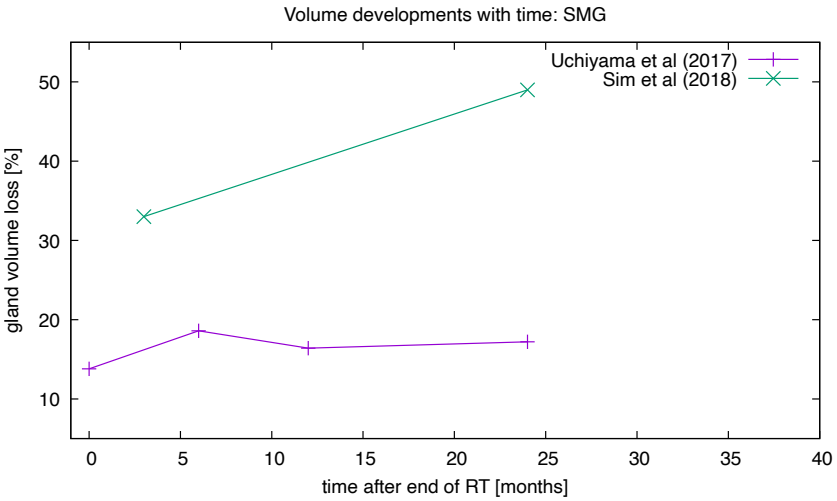


Figure 2.2: Comparison of published data of the development of submandibular gland volume with time: Uchiyama et al[53], and Sim et al.[12].

We analyzed data from our collective for both parotid and submandibular glands with focus on volume changes as well as toxicities for up to 36 months after radiotherapy to find out if there is any recovery within these timeframes and compared them to the previously published data. Results can be found in Section 4.6 (Objective A3: Are gland volumes recovering?).

2.2.5 A.4: Are gland volumes changes related to the doses received during radiotherapy?

Decrease in gland function (measured directly via saliva flow or indirectly via xerostomia) during and after radiotherapy seems to be caused by multiple factors: Apoptosis (and subsequent decrease in gland volume), selective radiation damage to the plasma membrane of the secretory cells, and fibrosis[11, 31].

We examined the previously published data for changes in gland volume and found eleven papers including both volume changes in percent and mean doses for parotid glands.[12, 33, 40–44, 46, 48, 50, 51]

We found four papers including this kind of data for submandibular glands.[12, 46, 48, 51]

We aggregated the numbers we extracted from the papers listed above into one data file and generated two plots (one for PG, one for SMG data) and did linear regression on both to get an overview; the resulting plot is shown in Fig. 2.3.

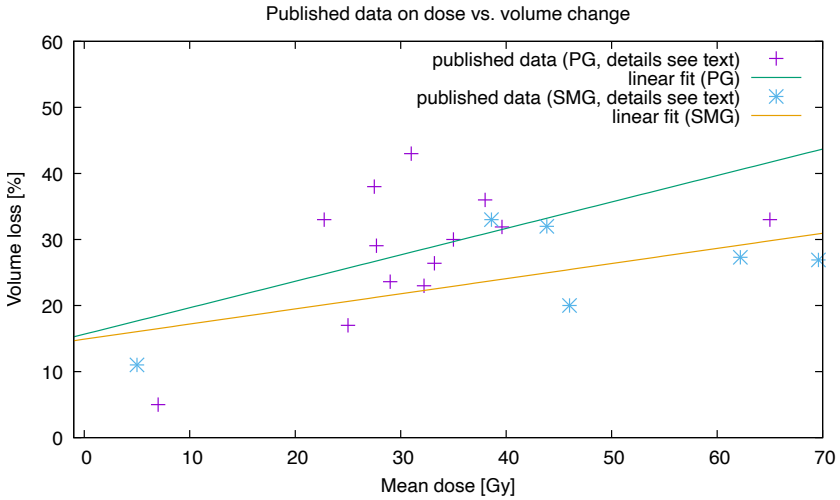


Figure 2.3: Comparison of published data of the development of parotid gland volume vs. mean dose:

We analyzed data from our collective for both parotid and submandibular glands with focus on possible correlations between volume changes and received mean dose for both parotids and submandibular glands. Results can be found in Section 4.7 (Objective A4: Are gland volume changes related to gland dose?).

2.2.6 A.5: Are gland doses different in each tumor location group?

Our patient collective includes six different tumor location groups (for details please see Section 4.2.3). In theory, some locations should be more exposed to radiation for simple anatomical reasons - tumors of the nasopharynx are closer to the parotids than tumors located in the larynx, for instance).

We analyzed received doses with respect to these tumor location groups. Comparison of our data to previously published was not reasonably possible. Although there usually is information provided on the tumor location in published studies, it was not specific enough to compile groups similar to ours from them for comparison.

Results can be found in Section 4.8 (Objective A5: Gland doses and tumor location groups).

2.2.7 A.6: Are changes in gland volume different in each tumor location group?

We analyzed received doses and gland volume changes with respect to our tumor location groups to identify possible correlations. Comparison of our data to previously published was not reasonably possible for the same reasons as described in Subsection 2.2.6 above.

Results can be found in Section 4.9 (Objective A.6: Gland volume vs.tumor location group).

2.2.8 A.7: Are changes in gland volume different in treatment groups?

Our patient collective contained patients who received both chemotherapy (CT) and RT as well as patients who only underwent radiotherapy. We analyzed changes in gland volumes with respect to these different groups to identify possible correlations.

Results can be found in Section 4.10 (Objective A.7: Gland volume vs.treatment groups).

We screened the publications of gland volume changes used in all our objectives above for concurrent information about whether the patients received radiotherapy only, or chemotherapy in parallel. Five studies did not provide any information about concurrent chemotherapy.[16, 17, 19, 34, 36, 41, 42] Two of them included only patients without concurrent chemotherapy.[14, 53] The majority of the studies included either patients with both radio- and radiochemotherapy.[5, 12, 33, 35, 37–40, 43–52]

None of them looked for differences between these two groups and the data in the majority of the studies shows quite a lot of variation regarding the ratios between RT and RCT patient numbers. We concluded that comparison to published data regarding this objective is not reasonably possible at this moment.

2.2.9 B.1: How are toxicities developing after radiotherapy?

Toxicities, especially xerostomia, are correlated to loss in salivary gland function which is expected to occur during and after radiotherapy. [9, 18, 26]

Besides apoptosis, selective radiation damage to the plasma membrane of the secretory cells and fibrosis are also discussed for causing toxicities. [11, 31]

Dysphagia after radiotherapy is “comprised of a broad spectrum of structural, mechanical, and neurologic deficits”[58]. Many publications about the development of dysphagia after radiotherapy either focus on different endpoints (dependency on PEG or feeding tube, for instance) or scores other than the one used in this thesis[3] (examples include the University of Washington Quality of Life Scale or the EORTC Head and Neck 35 swallowing symptom score).[60–62] A recent review

[3] This thesis uses the Common Terminology Criteria for Adverse Events (CTCAE)[59].

article about reducing xerostomia and dysphagia after radiotherapy in patients with head and neck cancer also included no references with comparable scoring.[15]

We concluded that comparison to published data regarding dysphagia is not reasonably possible at this moment.

Research about xerostomia after radiotherapy in patients with neck cancer addresses a broad range of endpoints: Saliva flow (SF), quality of life, weight loss, and dental problems.[7, 8, 10–12, 15, 16, 26, 27, 62–75]

We identified fifteen recent publications about the development of xerostomia after radiotherapy using CTCAE scores.[12, 15, 62, 63, 65–75] Thirteen of them contained sufficient information (actual numbers, not only plots of the data or similar) we could use for comparison with the our patient collective.[12, 63, 65–75]

The published data mentioned earlier includes information from various timeframes from during radiotherapy to just after end of it, and up to a maximum of almost 40 months after end of radiotherapy (39 months, provided in [75]). Most of them provide data about up to 24 months after end of radiotherapy.[12, 66, 67, 69–72] Others range in the timeframe in between (0–18 months) or, rarely, include multiple points in time.[12, 63, 65, 68, 69, 73, 74]

Four studies provided only aggregated data: Either the percentages of patients with xerostomia grade <2, or grade ≥ 2 [63, 65]; or percentages of patients with xerostomia grade ≥ 3 [66, 73].

There is rarely any data about the development of xerostomia with time including multiple data points. Two studies included xerostomia data at at least two data points: Just after end of radiotherapy (0 months) and at 24 months [69]; and at 0, 3 and 24 months [12].

An overview about the data available for comparison from the publications mentioned above is provided in Table 2.1 below.

We analyzed toxicities (xerostomia and dysphagia) in our patient collective to determine if there are significant differences in those between pre- and post radiotherapy as well as if there is any recovery within 12 (24, 36) months.

Results can be found in Section 4.11 (Objective B.1: Toxicity development).

Table 2.1: Previously published xerostomia data for various time frames. G = Grade of xerostomia (CTCAE)

Time [months]	G0 [%]	G1 [%]	G2 [%]	G3 [%]	G4 [%]	Source
0	8	8	0	0	0	[69]
0	0	55	45	0	0	[12]
3	0	45	36	18	0	[12]
12	25	42	32	0	0	[74]
12	52	14	30	3	0	[68]
24	50	50	0	0	0	[72]
24	66	32	2	0	0	[67]
24	5	87	8	0	0	[70]
24	0	0	8	0	0	[71]
24	5	20	2	0	0	[69]
24	0	40	53	7	0	[12]
39	0	24	19	1	0	[75]

2.2.10 B.2: Are toxicities related to tumor location groups?

We analyzed toxicities (xerostomia and dysphagia) in our patient collective to determine if there are significant correlations with tumor location groups.

Most studies mentioned in Section 2.2.9 above focused on patients with nasopharyngeal carcinoma.[12, 62, 66–68, 70–75] Some include tumors of the oropharynx.[62, 63] Others only mention tumors of head and neck without further detail.[15, 64, 65, 69]

Comparison of our data to previously published was not reasonably possible. Although there usually is information provided on the tumor location in published studies, it was not specific enough to compile groups similar to ours from them for comparison.

Results can be found in Section 4.12 (Objective B.2: Toxicity versus tumor location groups).

2.2.11 B.3: Are toxicities different in treatment groups?

We analyzed toxicities (xerostomia and dysphagia) in our patient collective to determine if there are significant differences between treatment groups (RT vs. RCT).

Results can be found in Section 4.13 (Objective B.3: Toxicity versus treatment groups).

The data in the majority of the studies about toxicities after radiotherapy (RT) or radiochemotherapy (RCT) shows a lot of variation regarding the ratios between RT and RCT patient numbers. We concluded that comparison of our results to published data regarding this objective is not reasonably possible at this moment.

2.2.12 B.4: Are toxicities related to gland volume changes?

We analyzed toxicities (xerostomia and dysphagia) in our patient collective to determine if there are significant correlations with the changes in gland volumes.

Results can be found in Section 4.14 (Objective B.4: Toxicity versus gland volume changes). We could not find sufficient data for comparison.

2.2.13 B.5: Are toxicities related to received doses?

We analyzed xerostomia and dysphagia in our patient collective to determine if there are significant correlations with the received gland doses.

Only one study of the publications mentioned earlier also included details about gland doses, although with grouped toxicity data (percentages of patients with xerostomia grade <2, or grade ≥ 2). It stated that six months after end of radiotherapy the group of patients who reported grade <2 xerostomia had received a mean dose of 22 Gy; patients who reported grade 2 or higher xerostomia had received a mean dose of 34 Gy.[63]

There is no information about the dose received by each gland. A comparison to our results is therefor not reasonably possible.

Results can be found in Section 4.14 (Objective B.4: Toxicity versus gland volume changes).

Chapter 3

Material and Methods

3.1 Study Design

We used a retrospective observational study, a variant of a cohort study that is appropriate when patient data is screened retrospectively for specified exposure and outcome within a defined cohort.

We compared a patient's organ-specific exposure to radiation during radiotherapy with the same patient's volume changes for the organs in question as well as his/her experienced toxicities (xerostomy, dysphagy and others) during follow-up.

3.2 Setting

During this study, we recruited patients with head and neck tumors treated curatively with RT or combined radio- and chemotherapy (RCT) at the institute for radiotherapy at the University Hospital Regensburg (*Uniklinik Regensburg*, abbreviated as UKR below) who started treatment between 2011 and 2015 aged 18 and above. Follow-ups were targeted at 6-weeks, 3-months, 6-months and 12-months intervals starting with the end of each patient's radiotherapy.

3.3 Participants

3.3.1 Stage I: Potentially Eligible Candidates

Whenever treatment is planned at the UKR radiotherapy department for a specific patient, this patient is added to our monthly list of new patients (called "Neueinstellungen"). For each accelerator (L1, L2, L3 and Primus II) new patients are recorded, their treatment is calculated and documented. The records include the patient's name, birth date, diagnosis, area treated, and the date the patient was added.

We screened potential study candidates using these lists and added every patient meeting the inclusion criteria listed above to our list of potentially eligible study candidates during stage one.

3.3.2 Stage II: Examination of Eligibility

During stage two we examined this list of potentially eligible candidates matching the exclusion criteria listed below.

The following criteria were used to remove candidates from the list of potentially eligible study candidates during stage two:

- Patients with tumors of the salivary glands
- Patients with cancer of unknown primary (CUP)
- Patients treated for palliative purposes (initially or after treatment started)
- Patients who did not follow up for at least one year at our institute
- Patients who aborted treatment

Palliative treatment

Patients with palliative treatment regime were excluded, both for initially palliative care and care regimes changed from primary or adjuvant to palliative during treatment (within twelve months). Palliative treatment differs substantially from primary or adjuvant treatment so comparability to standard treatment is not ensured in these cases.

Tumors of salivary glands and CUP syndrome

The main objective of this study was to look at correlations between salivary gland volumes and applied dose. In case of tumors of the salivary glands itself this makes no sense so these patients were excluded from the beginning. We also excluded patients with CUP syndrome for similar reasons.

Aborted treatment

Patients abort treatment for a variety of reasons. The most common reasons include major toxicity effects (patients did not tolerate treatment) as well as side issues (infected percutaneous endoscopic gastrostoma (PEG) devices, sepsis, pneumonia, and others).

Missing follow-ups

Patients who did not follow up properly (for at least one year) were excluded.

3.3.3 Stage III: Confirmation of Eligibility

Finally, during stage three, we confirmed eligible candidates by screening available imaging data for the dates of their follow-ups.

The following criteria were used to confirm candidates for eligibility:

- Existing imaging data (CT, or MRT) for at least two dates: One before treatment, and at least one more at either 1, 3, 6, or 12 months after end of radiotherapy
- Imaging includes full range of parotid and submandibular glands

3.4 Bias

Detection bias caused by missing records due to poor follow-up could influence the association between applied dose and both gland volume and toxicity variables. Eventually patients feeling well and experiencing less toxicities are less likely to show for follow-ups.

3.5 Study Size

The number of cases in the area during the study size determined the original sample size. The number of patients meeting the eligibility criteria as described above determined the final sample size.

3.6 Variables

For each patient of the final patient collective we screened their patient records, their respective radiotherapy treatment plans and all available imaging data (CT and MRT) for the following variables:

A. **Demographic data:** ID, Date of birth, date of first diagnosis, gender

B. **Tumor related data:** ICD-10 code, TNM classification, staging and grading, histological markers

C. **Treatment details:** Radiotherapy (RT) and chemotherapy (CT) details like start and end of treatment, applied dose, etc. (details see below)

D. **Toxicity data:** Dysphagy, xerostomia, mucositis (all before and after 1, 3, 6 and 12 months after end of RT) and dermatitis (before and after one months)

E. **Gland volume data:** Volumes of parotid and submandibular glands (each separate for both sides) before and after 1, 3, 6 and 12 months after end of RT

F. **Gland dose data:** DVH data for the parotid and submandibular glands (each separate for both sides)

All demographic, tumor related, treatment, toxicity data was extracted from the hospital's patient records. Data for individual gland doses was extracted from our radiotherapy planning software (OnCentra). The Common Terminology Criteria for Adverse Events (CTCAE) system[59] has been used for toxicity grading.

Gland volumes were determined by importing all available imaging data (CT and MRT) for the patients in question into our radiotherapy planning software (OnCentra). For each DICOM[1] set, relevant organ structures were defined in the planning software and their volumes recorded.

Gland doses were determined by exporting dose-volume-histograms (DVH) files from our radiotherapy planning software OnCentra. We exported one DVH file per gland (minimum: two - left and right parotid; Maximum: four, both parotids as well as left and right submandibular).

The DVH files include two columns (dose D_i and volume V_i) divided into $n = 200$ bins each ($i \in [1, 200]$ and volume from 100% to zero, divided into equal bin sizes) for each gland considered. The mean doses per gland $\bar{D}$ were calculated using equation 3.1.

$$\bar{D} = \frac{1}{n} \sum_{i=1}^{n} D_i \tag{3.1}$$

Specific data for dose per gland volume fractions (detailed DVH data) were also extracted from these files. These datasets have been used to calculate the mean gland doses used in sections 4.7, 4.9, and 4.15.

3.7 Quantitative Variables

3.7.1 Tumor Location

Tumor locations were divided into six groups based on their locations (determined by ICD-10 codes in the patient records) as listed in Tab. 3.1: MUN (ICD-10 codes C01-C05), ORO (C09), NAS (C11-C12), HYP (C13), LAR (C32) and MULTI (more than one single location).

[1] Digital Imaging and Communications in Medicine
[2] At least two or more of the ICD-10 codes listed in Table 3.1

Group Name (ID)	ICD-10 code	Location
MUN (1)	C01 C02 C04 C05	base of tongue other and unspecified parts of tongue floor of mouth palate
ORO (2)	C09	tonsil
NAS (3)	C11 C12	nasopharynx pyriform sinus
HYP (4)	C13	hypopharynx
LAR (5)	C32	larynx
MULTI (6)	CM^2	multiple

Table 3.1: Variables: Tumor location groups

3.7.2 Timeframes for Imaging Data

Follow-up dates were not always in perfect coherence with our desired intervals of 1, 3, 6, and 12 months after end or RT. In fact, follow-up dates including imaging data were so variable we needed to decide on cutoffs for each timeframe. We decided to use the following cutoffs (also listed in Tab. 3.2 below): One month (less than 55 days), three months (between 55 and 120 days), six months (between 120 and 241 days) and twelve months (241 days or more).

Timeframe [days]	Range d [days]
1 month	$d < 55$
3 months	$55 \leq d < 120$
6 months	$120 \leq d < 241$
12 months	$d \geq 241$

Table 3.2: Cutoff values [days] for follow-up time frames.

We had more data than expected for follow-ups greater than 12 months. We decided to look at two additional groups with timeframes 12–24 months and > 24 months additionally to the timeframes mentioned above to explore possible gland volume recoveries.

3.8 Evaluation & Statistical Methods

We used Pandas[21] for representing and analyzing data, NumPy[76] for basic numerical computation, SciPy[77] for scientific computation including statistics, R[22] for statistical analysis, and Matplotlib[78] for visualization.

The Python[20] programming language was used for all programming during this thesis.

If not stated otherwise, "correlation" refers to Pearson's correlation coefficient, "associations" are quantified as odds ratios, and statistical hypothesis testing has been performed using either t-tests, Kruskal-Wallis or ANOVA (details see below).

Where appropriate, data was analyzed for normality using both the Shapiro-Wilk test as well as D'Agostino's K-squared test. For data with assumed normal (Gaussian) distribution we used parametric tests (ANOVA). For data where we could not assume a normal distribution we used non-parametric tests (Kruskal-Wallis). Details can be found in the corresponding sections in Chapter 4.

3.8.1 Data Import and Conversion

All data collection (except for gland doses, for details on these please see below) happened manually and entered into an Excel file containing one sheet per variable group (patient data, radiotherapy, chemotherapy, toxicity, gland volumes, and imaging data metadata). This Excel file was imported and converted into a Pandas[21] data frame using the Python[20] programming language.

3.8.2 Data Analysis

This data frame has been analyzed and cleaned using Python[20] and Pandas[21] and was then analysed using R[22].

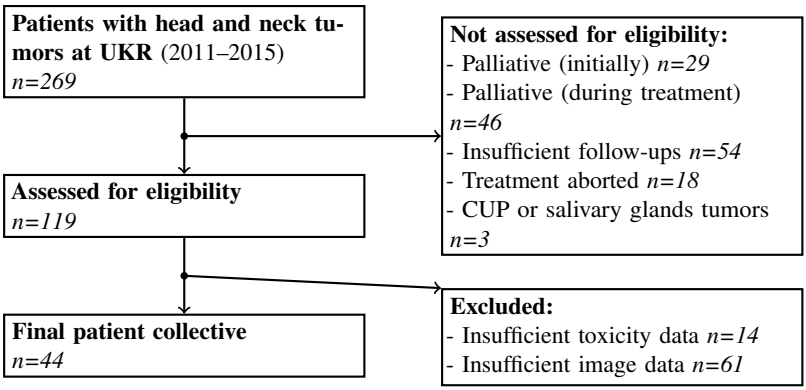
Chapter 4

Results

4.1 Participants

We identified a total of 269 patients matching the inclusion criteria. From these 269 patients a total of 150 were excluded because they either entered palliative treatment after therapy had started, were lost to follow-up or treatment was canceled[1].

Out of the 119 remaining patients 75 were excluded because of insufficient imaging or toxicity data. The final patient collective contained 44 patients.



[1] Cancellation of treatment had multiple reasons: toxicity too high, related (PEG infections, other like pneumonia, sepsis) or unrelated (personal decisions, additional health issues not related to the initial tumor) reasons

4.2 Descriptive Data

4.2.1 Demographics

The final patient collective contained $N = 44$ patients aged between 48 and 77 years ($\bar{x} = 62.8 \pm 7.8$ years). The majority (41) were male, three patients were female. The age distribution is shown in Fig. 4.1.

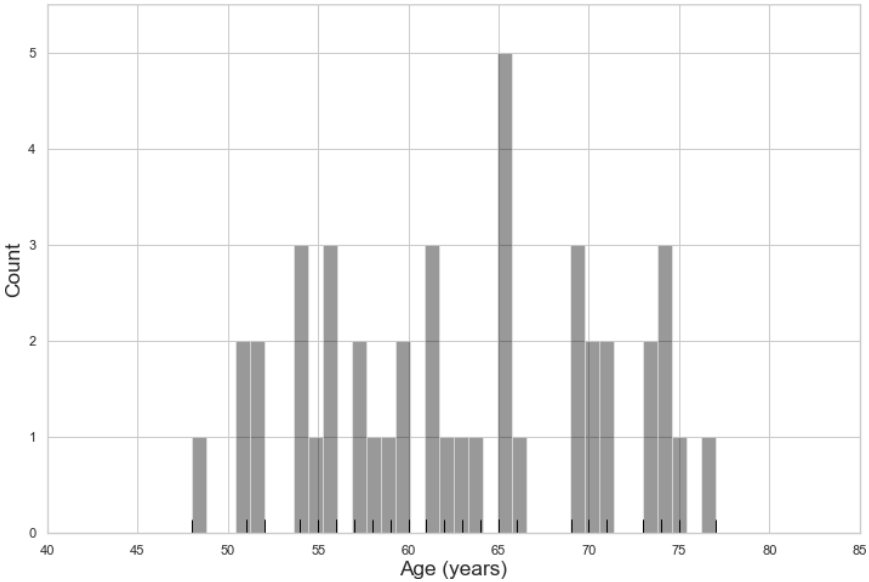


Figure 4.1: Age Distribution of our patient collective

4.2.2 Treatment

Eleven patients received adjuvant treatment and 33 were treated primarily. Thirty-one patients had both radio- and chemotherapy, 13 patients had radiotherapy only.

4.2.3 Tumor Location

Tumor locations were divided into seven groups as defined in Tab. 3.1 and previously described in section 3.7.1 above: MUN (ICD-10 codes C01-C05), ORO (C09), NAS (C11-C12), HYP (C13), LAR (C32) and MULTI (more than one single location).

The number of patients in each group are listed in Table 4.1 and shown in Fig. 4.2 below.

Group Name	Group ID	Patients
MUN	1	14
ORO	2	5
NAS	3	6
HYP	4	2
LAR	5	11
MULTI	6	6

Table 4.1: Numbers of patients in each tumor location group

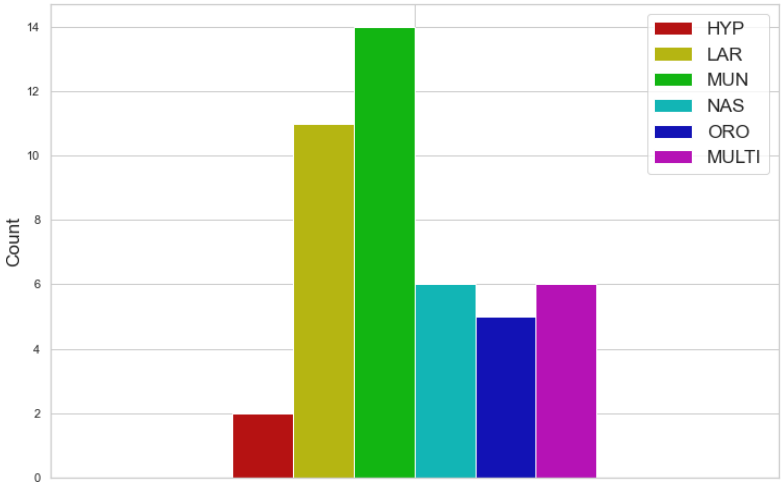


Figure 4.2: Distribution of tumor location groups in our patient collective

4.3 Outcome Data

Gland volumes could not be measured for all participants, all glands, and at all times. An overview about existing and missing data is presented below. Table 4.2 lists the number of available data sets for each gland and each point in time.

We had data available for follow-ups later than 12 months after end of RT as mentioned in Section 3.7.2:

24 out of 44 patients provided data from follow-ups later than 12 months after RT, 15 patients provided data from follow-ups 18 months or later, eight patients for 24 months and later, three for 30 months or later and two patients provided data for 36 months after end of radiotherapy. Details are listed in Table 4.3 below.

	PAL	PAR	SML	SMR
before RT	44	44	27	27
1 month	17	17	12	12
3 months	13	13	8	8
6 months	20	20	12	12
$\geq$ 12 months	31	31	12	12

Table 4.2: Number of valid datasets for each gland volume before and after 1, 3, 6, and 12 months after end of RT. PAL: left parotid; PAR: right parotid; SML: left submandibular gland, SMR: right submandibular gland.

Timeframe	**Number of patients**
$>$ 12 months	24
$>$ 18 months	15
$>$ 24 months	8
$>$ 30 months	3
$>$ 36 months	2

Table 4.3: Number of patients with follow-up data at more than 12 months after ed of RT

4.4 Objective A1: Gland volumes before and after RT

The first question (objective A1) was whether gland volumes are different before and after RT. No quantifications of any kind were made at this point, the only question was if the of the glands were significantly different before and after RT.

For each of the four glands in question (left parotid gland (PL), right parotid gland (PR), left submandibular gland (SML), and right submandibular gland (SMR)) we compared their volumes before and after RT. The timeframe for "after RT" was between the end of RT and up to three months afterwards.

If data for the first timeframe (six weeks) was available, it was used. In case of absence but presence of the second timeframe (up to three months) the latter one has been used. Details about timeframes and how we chose them is described in section 3.7.2.

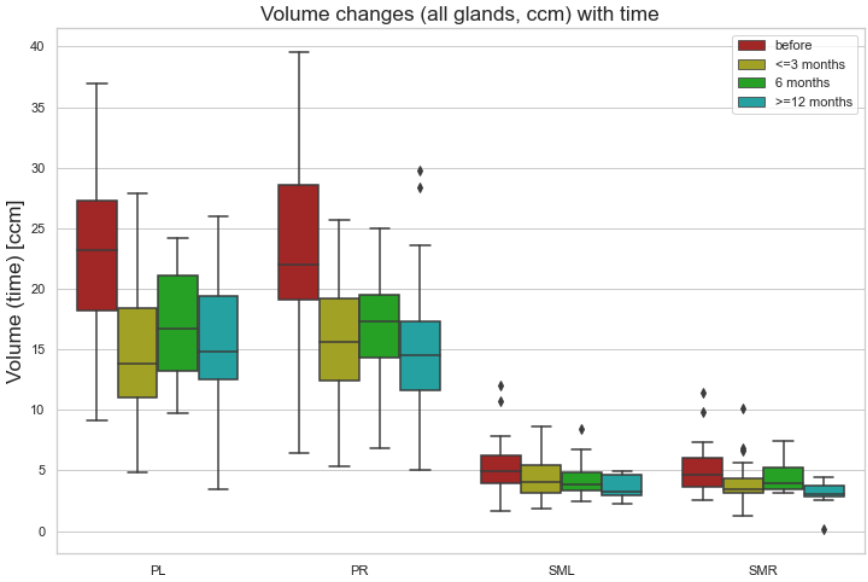


Figure 4.3: Gland volume changes with time for both parotids (PL, PR) and both submandibular glands (SML, SMR) - an overview

We used parametric tests for testing four sample pairs ("before" and "after" for each gland), our data turned out to be normally distributed (shown by QQ tests).

Figure 4.3 shows an overview of the development of all gland volumes in question with time.

As the volumes of the submandibular glands are much smaller than the parotid volumes for simple anatomical reasons we split up Figure 4.3 to get a better picture of each gland system: Figure 4.4 shows the development of the parotid glands (PL and PR), Fig. 4.5 the development of the submandibular glands (SML and SMR) before and after RT.

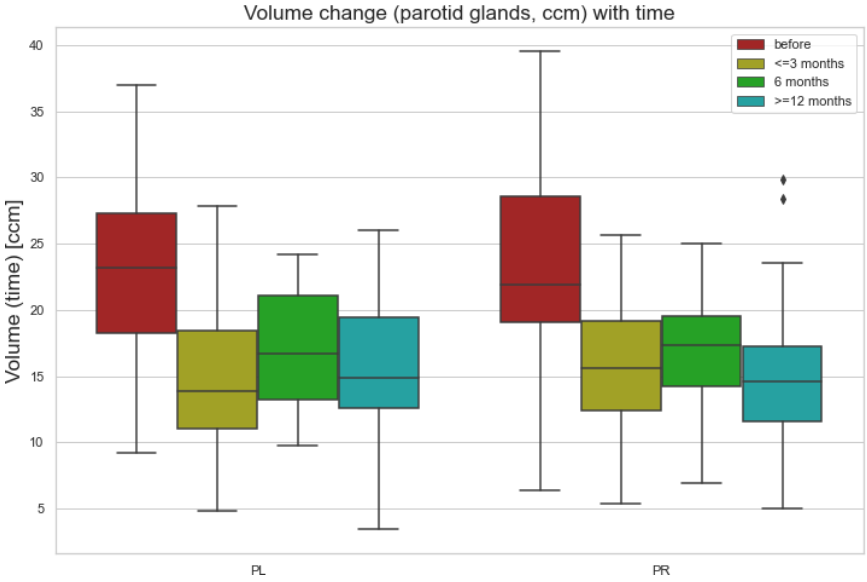


Figure 4.4: Gland volume changes with time for both parotid glands.

Parotid gland volumes are significantly smaller after RT ($p < 0.0001$). Submandibular gland volumes are significantly smaller after RT, too ($p < 0.05$). Details are listed in Table 4.5.

We expected an overall volume loss comparing gland volumes before and after RT as stated in Section 2.2.2 (A.1: Are gland volumes different before and after

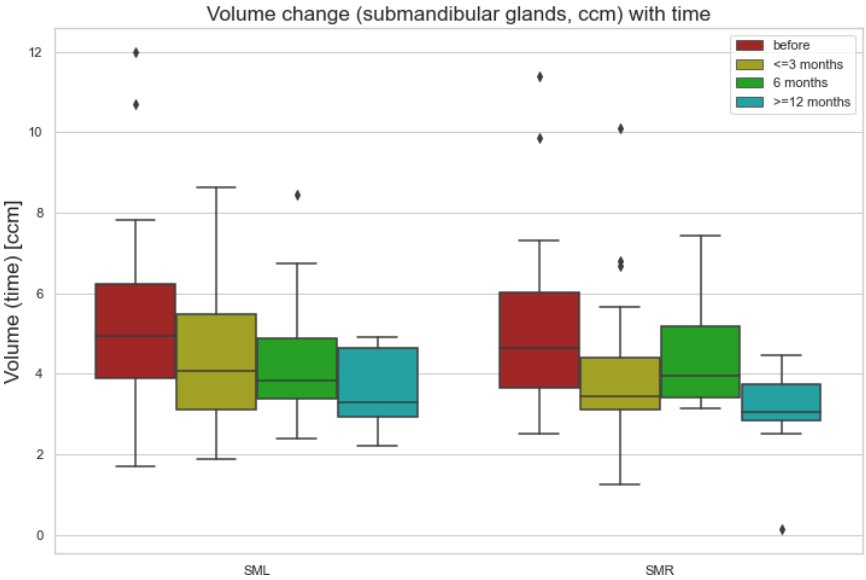


Figure 4.5: Gland volume changes with time for both submandibular glands.

Gland	$V_{t=0}$ [cm^3]	$V_{t\leq 3m}$ [cm^3]	$V_{t=6m}$ [cm^3]	$V_{t\geq 12m}$ [cm^3]
PL	23.33±6.85	15.26 ±5.75	16.96 ±4.53	15.35 ±5.71
PR	24.05 ±7.60	15.84 ±5.24	16.68 ±4.53	15.20 ±5.70
SML	5.37 ±2.31	4.46 ±1.70	4.39 ±1.70	3.60 ±0.94
SMR	5.12 ±2.07	4.11 ±2.16	4.32 ±1.27	3.10 ±1.13

Table 4.4: Mean value and standard deviation for all four gland volumes before ($t = 0$) and after RT ($t \leq 3$ months), 6 months, and $t \geq 12$ months

Gland	t	p-value	degrees of freedom
PL	-7.16	< 0.0001 (8.38^{-8})	25
PR	-7.98	< 0.0001 (1.22^{-8})	25
SML	-2.19	< 0.05 (0.02)	16
SMR	-1.92	< 0.05 (0.04)	16

Table 4.5: One sample t-test (H_0: $\bar{V}_{t\leq 3m} \geq \bar{V}_{t=0}$) for gland volumes before and after RT.

radiotherapy?), because volume loss of salivary glands during and after radiotherapy is well documented in literature as mentioned earlier. [5, 12, 14, 16, 19, 33–53]

Gland volume loss after radiotherapy has been confirmed by our research and in our specific patient collective for both parotid and submandibular glands.

4.5 Objective A2: Quantification of gland volume changes

The same setup as in objective [A.1] has been used. We compared the means of our four samples ("before" and "after" for each gland) and quantified them as percentages.

The average volume loss for the parotid glands was 34% of their original volume within the first three months.

Our results for the parotid glands are in good accordance with previously published numbers: As mentioned in section 2.2.3, according to literature mean PG volume decreases from baseline (before start of treatment) to after end of RT between 17% and 38% (mean: 28%). [5, 33, 35–40, 42, 43, 45–51].

The submandibular glands lost an average of 18% in the same timeframe.

Our results for the submandibular glands are also in good accordance with previously published numbers: According to previously published studies, mean SMG volume decreases are reported between 14% and 34% (mean: 23%) from baseline to after end of RT.[12, 14, 35, 46, 48, 51].

Gland volumes after six months were approximately at the same levels as post RT.

For both parotids gland volumes did not change much after $\geq$12 months. Both submandibular glands have significant lower volumes after $\geq$12 months in comparison to their volumes after six months post RT.

Details are provided in Table 4.6.

Gland	$\leq$ 3 months [%]	6 months [%]	$\geq$12 months [%]
PL	-35 $\pm$16	-27 $\pm$30	-34 $\pm$21
PR	-34 $\pm$31	-31 $\pm$40	-37 $\pm$25
SML	-17 $\pm$26	-18 $\pm$27	-33 $\pm$59
SMR	-20 $\pm$4	-16 $\pm$39	-39 $\pm$45

Table 4.6: Gland volume changes with time for both parotids and submandibular glands at $\leq$3 months, 6 months, and $\geq$12 months after end of RT

Figure 4.6 shows our relative gland volume changes in percent compared to recent gland volume changes in literature for the parotid glands.

Figure 4.7 shows our relative gland volume changes in percent compared to recent gland volume changes in literature for the submandibular glands.

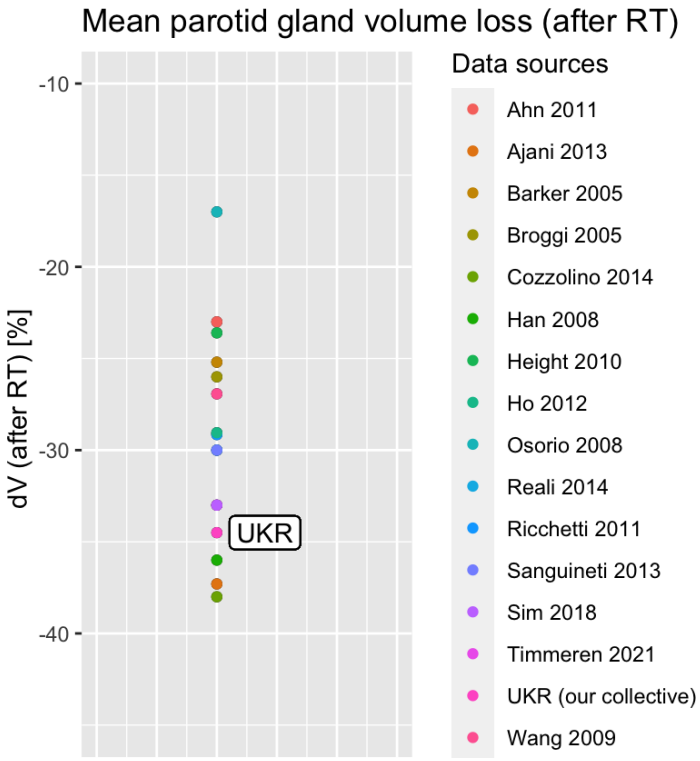


Figure 4.6: Gland volume changes at UKR (our patient collective) in comparison with gland volume changes described in recent publications: Parotid glands

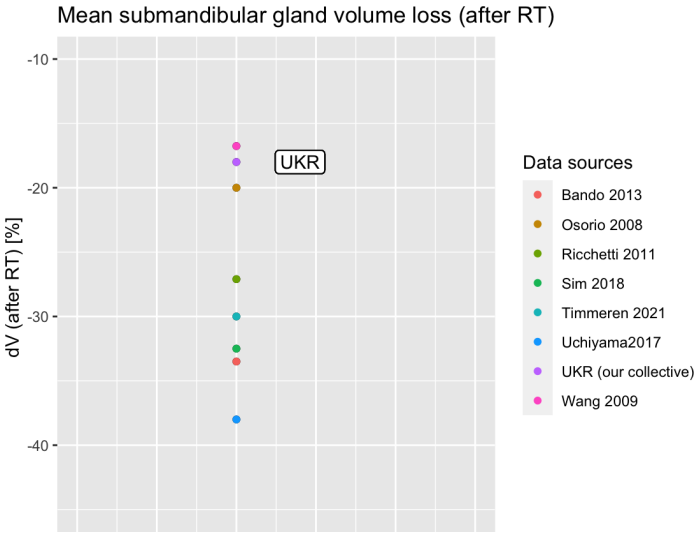


Figure 4.7: Gland volume changes at UKR (our patient collective) in comparison with gland volume changes described in recent publications: Submandibular glands

4.6 Objective A3: Are gland volumes recovering?

Mean gland volumes for $t = 0$ (initial gland volume before RT) and after 3, 12, 24, 36 months after end of RT are shown in Table 4.8 below.

Glands are considered to be in recovery if the difference $\Delta\bar{V}_t$ of gland volume at time t ($t \in (12, 24, 36)$ months) and the initial gland volume (at $t = 0$, "before" as above) is smaller than the difference $\Delta\bar{V}_{3m}$ between the gland volume at time $t = 0$ and after RT ($t = t \leq 3m$):

$$\Delta\bar{V}_t < \Delta\bar{V}_{3m}$$

with

$$\Delta\bar{V}_t = \bar{V}_t - \bar{V}_{t=0}$$

$$\Delta\bar{V}_{3m} = \bar{V}_{t\leq 3m} - \bar{V}_{t=0}$$

The calculated volume changes ΔV are listed in Table 4.7.

Gland	ΔV_{3m} [%]	ΔV_{12m} [%]	ΔV_{24m} [%]	ΔV_{36m} [%]
PL	-35 ±16	-34 ±25	-39 ±18	-33 ±3
PR	-34 ±31	-39 ±29	-39 ±24	-27 ±25
SML	-17 ±26	-32 ±59	-30 ±70	- [2]
SMR	-20 ±14	-31 ±69	-52 ±40	- [2]

Table 4.7: Gland volume changes for both parotids and submandibular glands at ≤3 months, 6 months, and ≥12 months after end of RT

Gland volumes are not significantly recovering for neither 12 (N=20) , 24 (N=9), nor 36 (N=3) months (all t-test p-values vary between 0.6 and 0.8 not allowing to reject the null hypothesis that the means are equal).

This result is in good accordance with data published in literature. As mentioned earlier (in Section 2.2.4), none of the recent publications show complete recovery to pre-treatment gland volumes.[12, 16, 52, 53]

An overview of the published data about parotid gland volume development with time is shown in Fig. 2.1 (Chapter 2).

[2] Not available (no data)

Gland	$V_{t=0}$ [cm^3]	$V_{t\leq 3m}$ [cm^3]	$V_{t=12m}$ [cm^3]	$V_{t=24m}$ [cm^3]	$V_{t=36m}$ [cm^3]
PL	23.33 ±6.85	15.26 ±5.75	15.64 ±5.27	13.98 ±6.70	17.09 ±1.78
PR	24.05 ±7.60	15.84 ±5.75	15.19 ±5.21	14.20 ±7.75	17.9 ±2.34
SML	5.37 ±2.31	4.46 ±1.70	3.78 ±1.03	3.07 ±0.25	- [2]
SMR	5.12 ±2.07	4.11 ±2.16	3.50 ±0.67	1.91 ±1.54	- [2]

Table 4.8: Gland volumes for both parotids and submandibular glands at $\leq$3 months, 6 months, and $\geq$12 months after end of RT

4.7 Objective A4: Are gland volume changes related to gland dose?

To verify if gland volume changes are related to gland dose, we compared the mean gland dose and the percentage of volume loss for both parotids and submandibular glands at time $t \leq 3m$ (less than three months). Additionally, we compared these values with focus on the average of all four glands and doses (also at the time $t \leq 3m$, less or equal than three months).

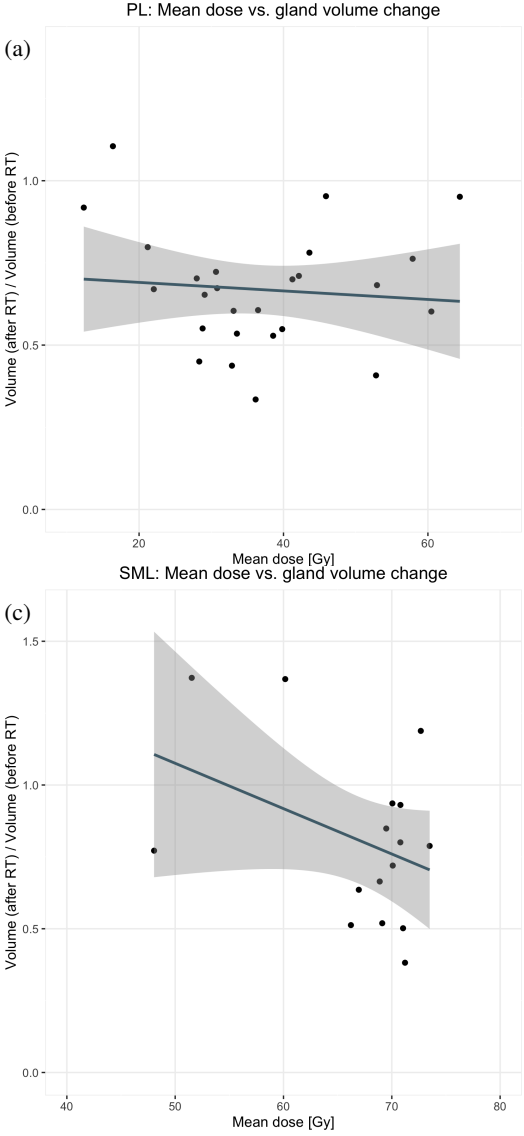
A linear regression of the average dose (D) versus gland volume (ΔV) resulted in an approximate prediction of $\Delta V = 0.96 - 0.004D$. The correlation is only weak, though (the Pearson correlation coefficient equals -0.13).

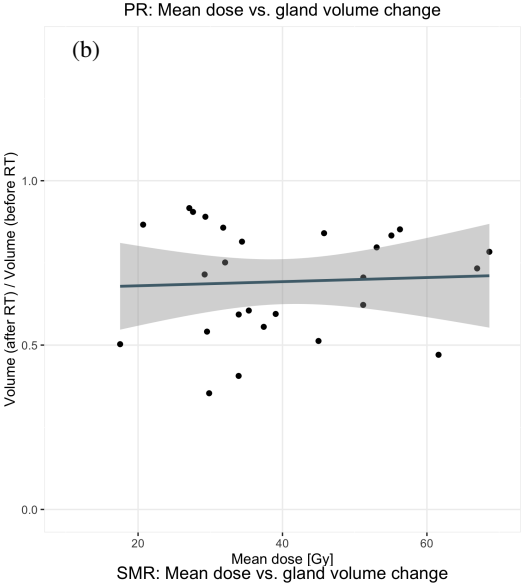
The Figures in Table 4.9 show our dose versus gland volume data and these linear regressions along with their margins of uncertainties. As one can easily see the uncertainties are quite large, so conclusions should only be drawn with caution.

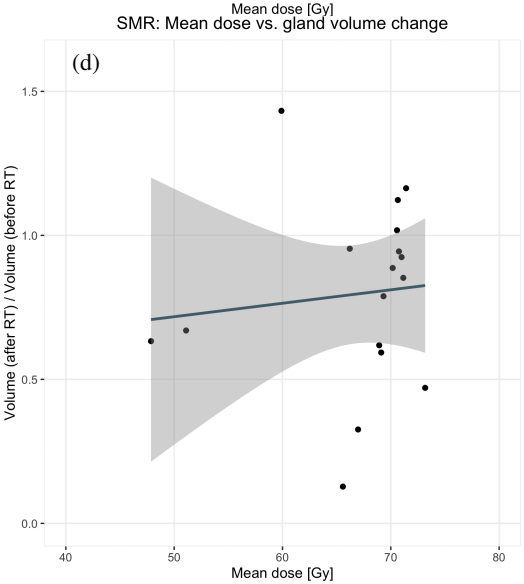
Figure 4.8 shows the combination respectively the average over all four glands and illustrates the resulting equation mentioned above ($\Delta V = 0.96 - 0.004D$): There seems to be a weak negative correlation between gland volume and dose, if at all.

To compare our results with the numbers published in literature we combined the data for both parotid glands (PG) into one file, and the data for both submandibular glands (SMG) into another one. In Section 2.2.5 we generated a data plot to get an overview about the published data (Figure 2.3).

Table 4.9: Gland volume changes vs. received dose: PL (a), PR (b), SML (c) and SMR (d)




PR: Mean dose vs. gland volume change
(b)
Volume (after RT) / Volume (before RT)
1.0
0.5
0.0
20
40
60
Mean dose [Gy]


SMR: Mean dose vs. gland volume change
(d)
Volume (after RT) / Volume (before RT)
1.5
1.0
0.5
0.0
40
50
60
70
80
Mean dose [Gy]

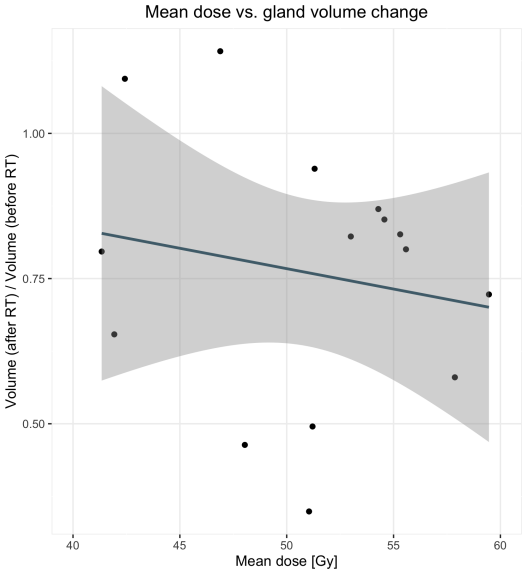


Figure 4.8: Gland volume changes vs. received dose (average)

Figure 4.9 below includes previously published data (with their corresponding linear fits), and our data described in detail above. As one can see comparison between the data sets - published vs. our data for both parotids and submandibular glands - is not reasonably possible, especially for the submandibulars.

The minimum of the mean dose on our data set for the SMG is 48 Gy, the published data includes much smaller gland doses. Variation of the mean dose in our data set is much smaller, which makes ist difficult to run a linear regression without getting large uncertainties (Figures 4.9 to 4.8 show these - the areas in light grey - clearly).

The uncertainties of the mean dose vs, gland volume changes for the PG are smaller than the ones for the SMG, nevertheless they are still too large to draw any conclusions. A comparison therefor is not appropriate.

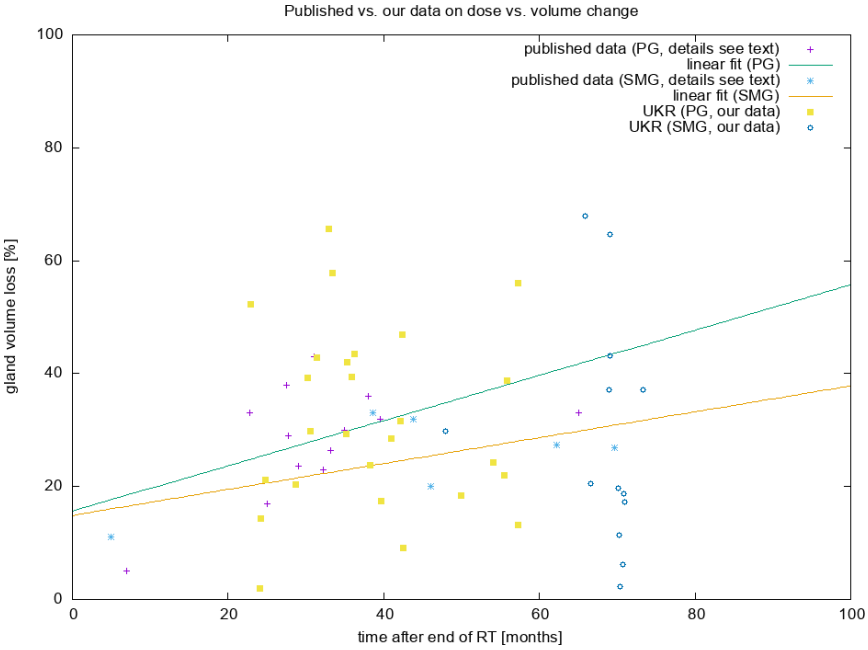


Figure 4.9: Comparison (published data vs. ours) of gland volume changes vs. received dose (average)

4.8 Objective A5: Gland doses and tumor location groups

This section aims to answer the question if there are any differences in received dose in the different tumor location groups as introduced in Tab. 4.1.

Salivary glands received a total average dose of 51.63 Gy (all glands, all groups). The received doses per group are shown in Fig. 4.10. To clarify differences between tumor location groups, Fig. 4.11 shows the difference between the received doses per group and the average gland dose (please note the different y-axis).

Their corresponding numeric values are provided in Tab. 4.12.

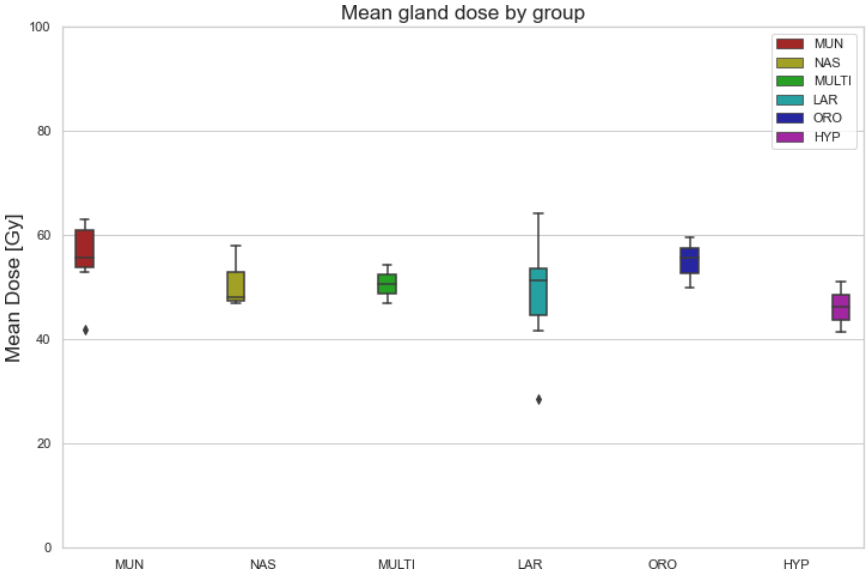


Figure 4.10: Mean gland doses for different tumor location groups - total dose

At first glance, the results shown in Tab. 4.12 and Fig. 4.11 suggest that gland doses were higher than average for patients with tumors in the oral region (MUN[3]

[3]For details on the different tumor location groups please see Table 4.1

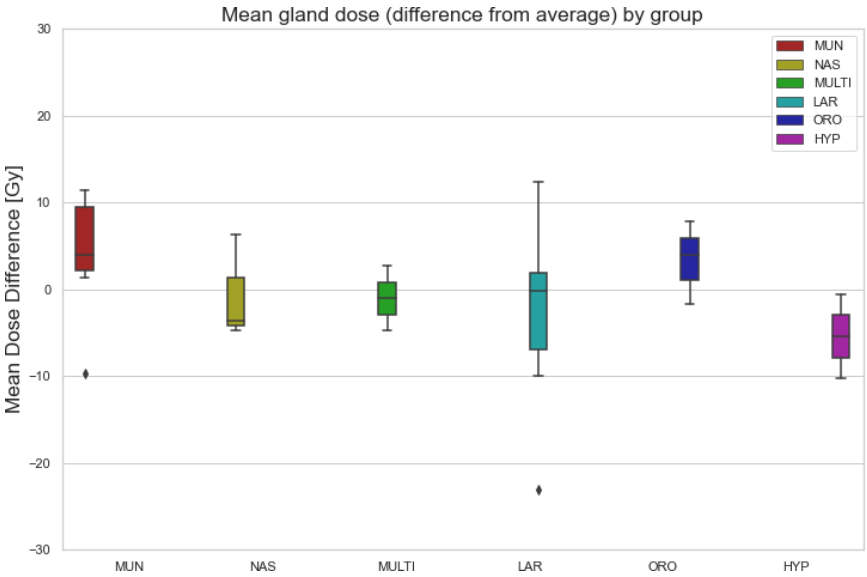


Figure 4.11: Mean gland doses for different tumor location groups - difference from gland average (51.63 Gy)

and ORO[3] groups) and lower for the tumors in the cervical regions like HYP[3] group.

Average gland doses - a mean over all four salivary glands in question - is not an appropiate measure, though. During treatment planning the parotids are defined as regions of interest (and thus spared as much as possible); the submandibular glands are not. This results in a generally higher dose to the submandibular glands.

To address this issue we took a look at the distribution for each gland separately. Mean doses were 38.08 Gy for the parotids and 66.67 Gy for the submandibular glands. Mean doses per gland and by group are shown in Fig. 4.12 and listed in Tab. 4.13.

All units in Tab. 4.13 are in Gy, the delta term (Δ) in this table refers to the difference from the apropiate mean value. The group called ALL refers to an average over all groups.

Group	Mean dose [Gy]	Difference to average dose [Gy]
MUN	55.73	+4.10
NAS	50.93	–0.70
MULTI	50.59	–1.04
LAR	49.27	–2.36
ORO	54.97	+3.34
HYP	46.19	–5.44

Table 4.12: Mean gland doses and deviations from overall average by tumor location group

Group	PL	PR	SML	SMR	ΔPL	ΔPR	ΔSML	ΔSMR
ALL	37.19	38.97	66.94	66.38	-0.89	+0.89	+0.28	-0.28
MUN	41.85	40.38	67.10	67.03	+3.78	+2.30	+0.44	+0.37
ORO	41.58	42.41	65.09	66.82	+3.51	+4.33	-1.57	+0.16
NAS	32.42	33.12	65.66	65.55	–5.66	-4.95	-1.00	-1.11
HYP	32.47	31.89	61.37	59.04	-5.61	-6.19	-5.29	-7.62
LAR	27.68	35.66	67.12	66.79	-10.39	-2.42	+0.46	+0.13
MULTI	46.40	47.07	72.82	69.95	+8.32	+8.99	+6.15	+3.29

Table 4.13: Mean gland doses and deviations from overall average by tumor location group.

Fig. 4.12 shows a comparison of total doses per gland and group and the difference from average gland dose by group for both parotid and submandibular glands.

The parotids received 38.08 Gy on average. The data suggests that eventually the parotids in the MUN, ORO and MULTI groups received more than the average, and the NAS, HYP and LAR seem to have received less. The submandibular glands received 66.67 Gy on average. The mean dose in the HYP group appears to be less than the average, and in the MULTI group it looks like it could be greater.

The results of all tests are listed in Tab. 4.14 in the form p-value (df). The only significant differences we found for all glands and groups are the left parotid (PL) in the NAS ($p < 0.01$) and LAR groups ($p < 0.05$).

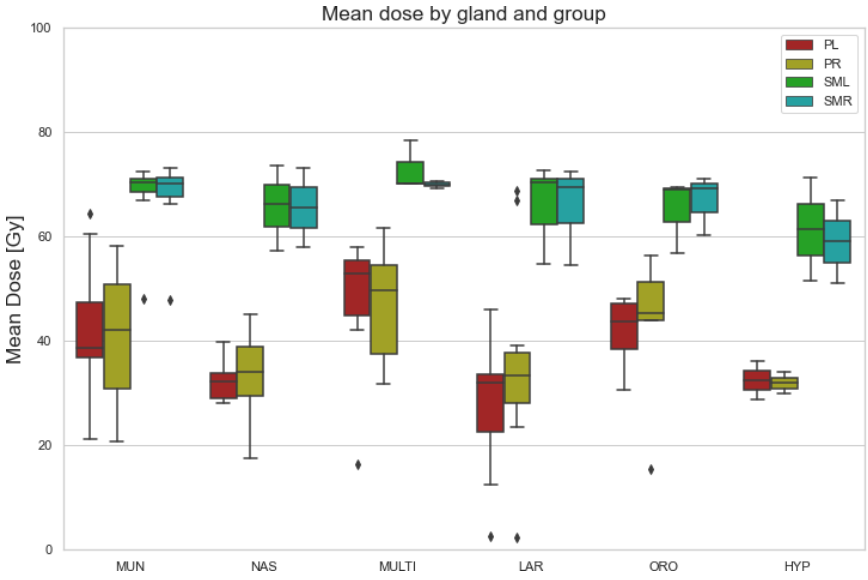


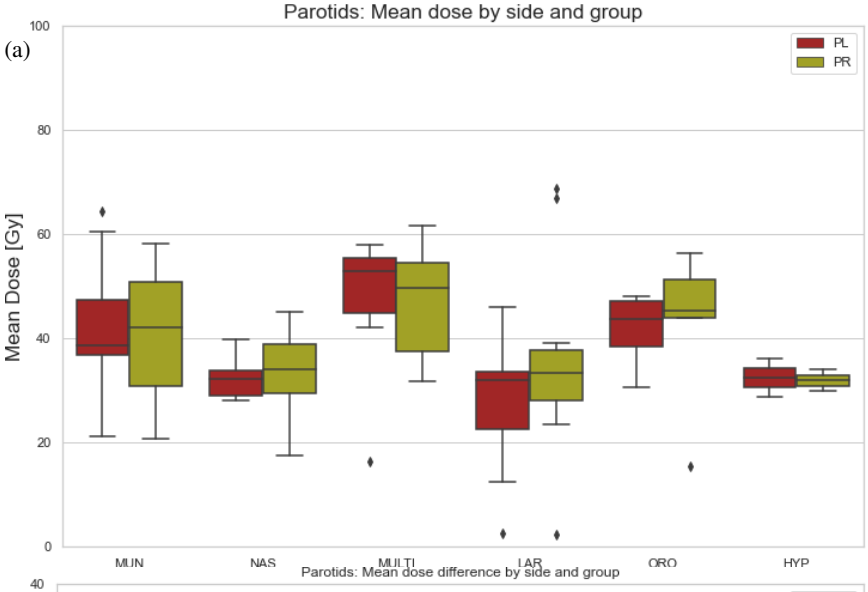
Figure 4.12: Average doses per gland for different tumor location groups

Group	PL	PR	SML	SMR
MUN	0.13 (13)	0.24 (13)	0.45 (6)	0.46 (6)
ORO	0.17 (4)	0.29 (4)	0.63 (2)	0.48 (2)
NAS	0.008** (5)	0.13 (5)	0.43 (2)	0.41 (2)
HYP	0.18 (1)	0.10 (1)	0.34 (1)	0.26 (1)
LAR	0.01* (10)	0.34 (10)	0.41 (9)	0.47 (9)
MULTI	0.13 (5)	0.06 (5)	0.08 (2)	0.06 (1)

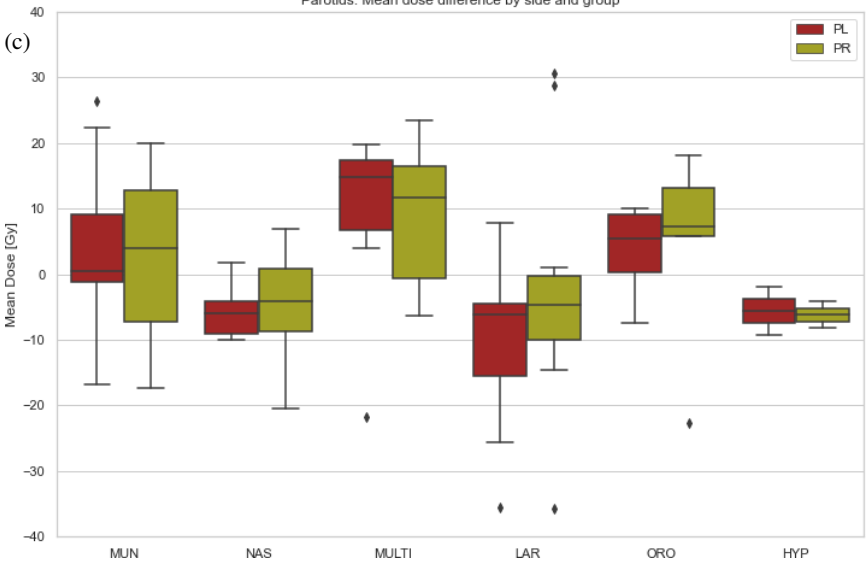
Table 4.14: T-tests for different groups and glands. All units are in the form p-value (df) for one-sided t-tests with significance levels of $p < 0.05$ (*) and $p < 0.01$ (**).

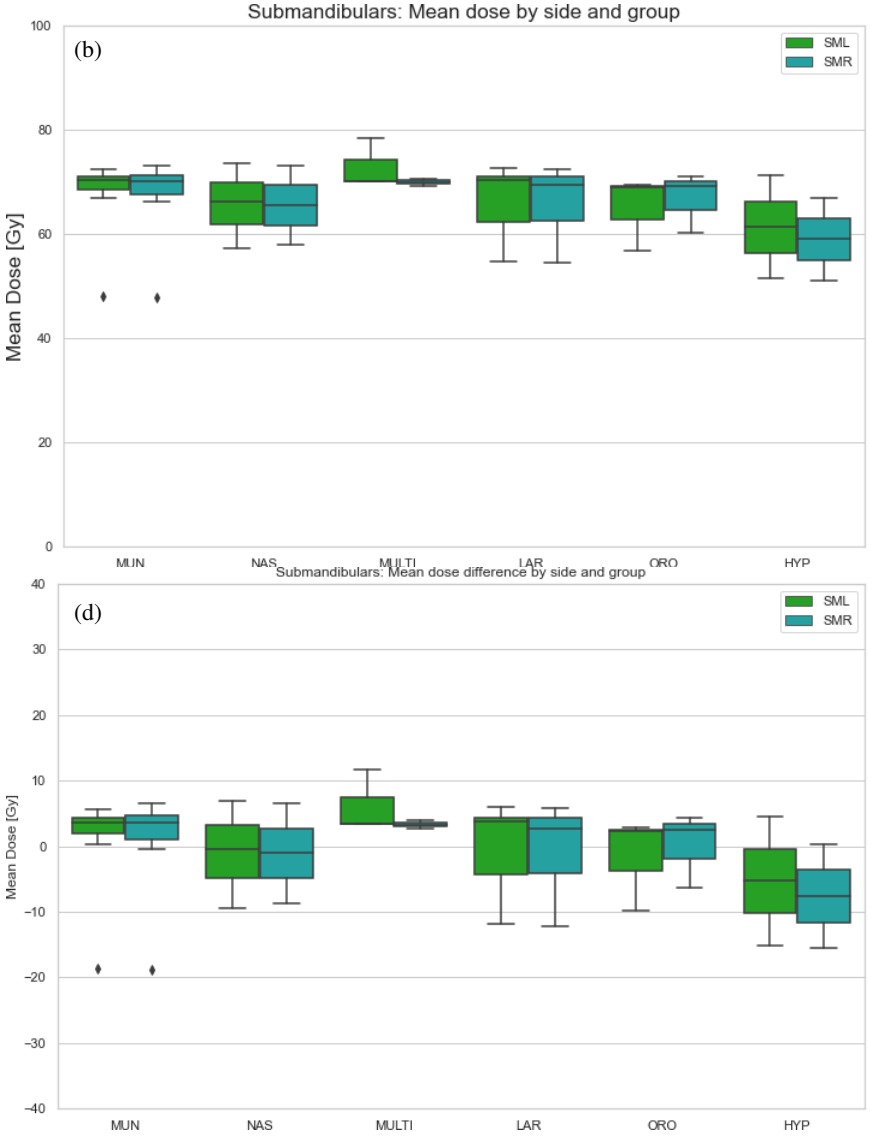
Table 4.15: Total doses per gland and group (a/b) and difference from average gland dose by group (c/d)

(a)



(c)




Submandibulars: Mean dose by side and group
(b)
SML
SMR
Mean Dose [Gy]
100
80
60
40
20
0
MUN
NAS
MULTI
LAR
ORO
HYP
Submandibulars: Mean dose difference by side and group
(d)
SML
SMR
Mean Dose [Gy]
40
30
20
10
0
−10
−20
−30
−40
MUN
NAS
MULTI
LAR
ORO
HYP

4.9 Objective A.6: Gland volume vs. tumor location group

The development of gland volume changes with time has already been discussed in sections 4.4 and 4.5. The objective of this section is to answer the question if there are significant differences of gland volumes before and after RT between tumor location groups.

Fig. 4.13 gives a first impression of wild variability in volume changes (before vs. after as above) between glands and groups. Especially for the submandibular glands the values vary and sometimes the gland volume is bigger after RT than before which is likely not a dose-related effect but caused by uncertainties in the measurement itself.

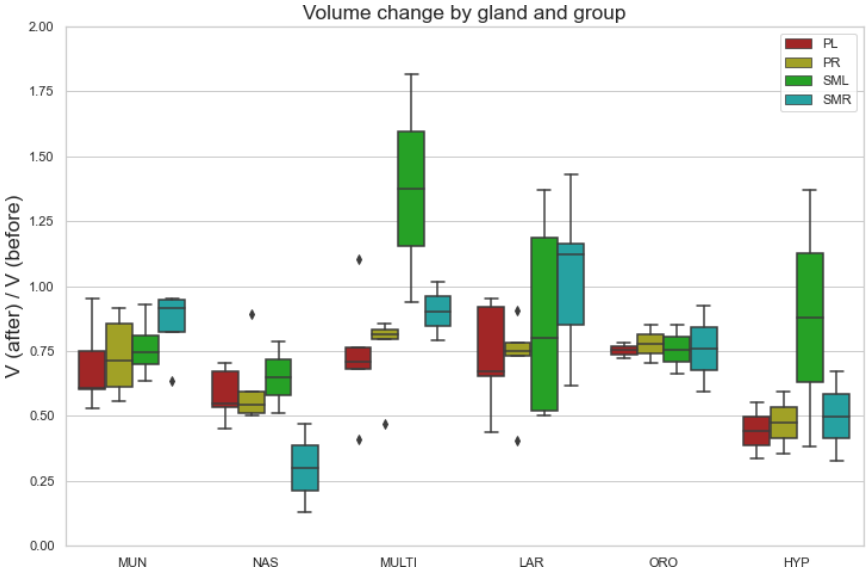


Figure 4.13: Volume changes after RT per gland for different tumor location groups

Submandibular glands are small by nature and errors in measurement have greater effect than for larger structures. In section 4.4 we could show that on average - over

all groups - submandibular glands are smaller after RT but the data clearly does not allow to draw conclusions when broken down to the level of different tumor location groups. For instance, there are only two patients with measurements for the volumes of both submandibular glands in the NAS, MULTI, ORO and HYP groups (and only four in the MUN and five in the LAR groups, respectively). There are not enough observations per group to analyze the data from submandibular glands properly. We therefor refrained from doing so.

Things look brighter when looking at the data from the parotids only, though - Fig. 4.14 provides an overview.

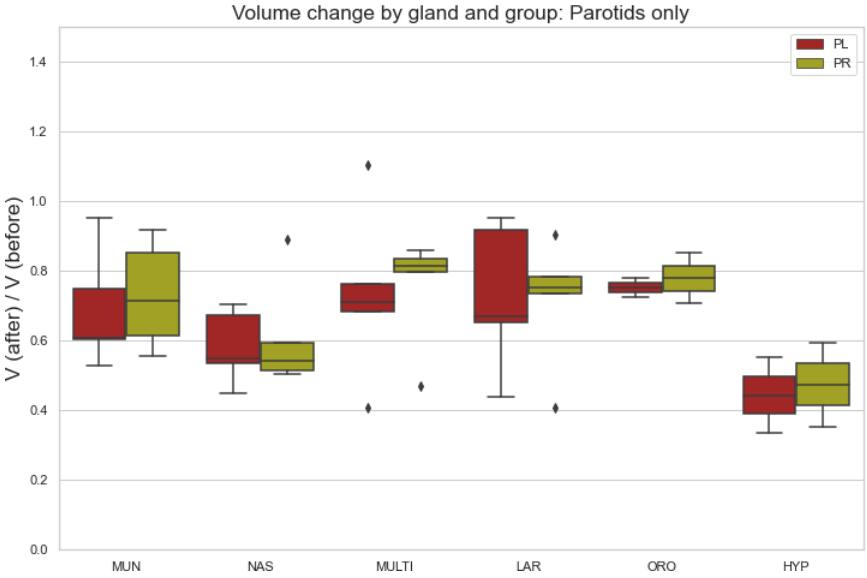


Figure 4.14: Volume changes after RT per gland for different tumor location groups (parotids only)

Looking at the ratios of gland volumes (after/before) listed in Tab. 4.18 it seems like the gland volume changes in the HYP group (both sides) and the ones in the LAR group (left side only) could be different from the average parotid gland volume changes. As sample sizes are relatively small for the parotids too these results have to be treated with caution.

Group	PL	PR	ΔPL	ΔPR	PG	ΔPG
MUN	0.68	0.73	-0.02	-0.02	0.71	0.00
ORO	0.75	0.78	+0.04	+0.07	0.77	+0.06
NAS	0.58	0.61	-0.13	-0.10	0.60	-0.13
HYP	0.44	0.47	-0.30	-0.27	0.46	-0.29
LAR	0.86	0.72	+0.12	-0.03	0.79	+0.04
MULTI	0.73	0.75	-0.01	+0.01	0.74	+0.00

Table 4.18: Gland volume changes (ratio after/before) and deviations from average change by tumor location group.

When looking closer, only the gland volume changes in the HYP group (both left and right parotid are smaller) and the left parotid in the LAR group are significntly smaller than the average ($p < 0.05$). Details are listed in Tab. 4.19.

Group	PL	PR	PG
MUN	0.34 (6)	0.66 (6)	0.50 (6)
ORO	0.19 (1)	0.26 (1)	0.23 (1)
NAS	0.03* (4)	0.12 (4)	0.05 (4)
HYP	0.11 (1)	0.13 (1)	0.12 (1)
LAR	0.76 (4)	0.38 (4)	0.72 (4)
MULTI	0.46 (4)	0.55 (4)	1.00 (4)

Table 4.19: T-tests for different groups and parotid glands. All units are in the form p-value (df) for one-sided t-tests with significance levels of $p < 0.05$ (*) and $p < 0.01$ (**).

We could therefor not conclude that there were any significant differences in gland volume changes in any of our tumor location groups. We suggest repeating the experiment with more patients to draw any further conclusions.

4.10 Objective A.7: Gland volume vs. treatment groups

Our patient collective contained patients who received both CT and RT as well as patients who only underwent radiotherapy. We analyzed changes in gland volumes with respect to these different groups to identify possible correlations.

The RT group only contained two values for the SMR and SMR glands. We therefor only analysed the values for both parotid glands. Fig. 4.15 provides an overview, Tab. 4.20 the corresponding results.

Group	PL	PR	ΔPL	ΔPR
ALL	0.67	0.69	-0.01	0.01
RCT	0.66	0.67	-0.02	-0.01
RT	0.76	0.84	+0.08	+0.16

Table 4.20: Gland volume changes (ratio after/before) and deviations from average change by gland and treatment group (RCT vs. RT only). ALL: average over both groups.

One-way ANOVA shows no difference between the means of gland volume ratio after/before between the two groups RT versus RCT neither for the left parotid ($p = 0.374$) nor the right parotid ($p = 0.101$). We therefor conclude the treatment (RT versus RCT) has no influence on changes in gland volume.

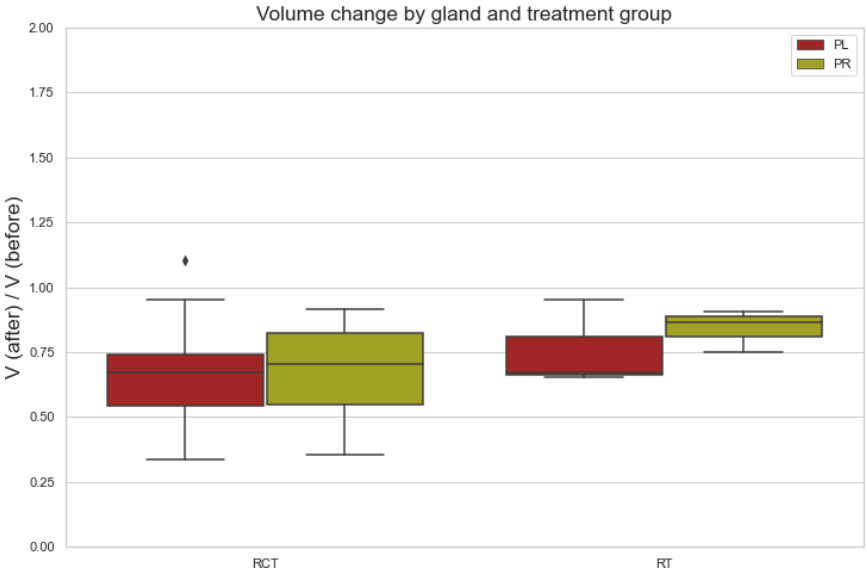


Figure 4.15: Volume changes after RT per gland for different treatment groups (RT vs. RCT)

4.11 Objective B.1: Toxicity development

We analyzed toxicities (xerostomy and dysphagia) in our patient collective to determine if there are significant differences in those between pre- and post radiotherapy as well as if there is any recovery within 12 months after end of RT.

4.11.1 Xerostomia

Xerostomia ranges from CTC grades zero to three (no grade four) with grade three only at six months after end of RT. Fig. 4.16 provides an overview about the development of xerostomia averages over time indicating a delayed onset of xerostomia - its starts after approximately thee months, not right after the end of RT.

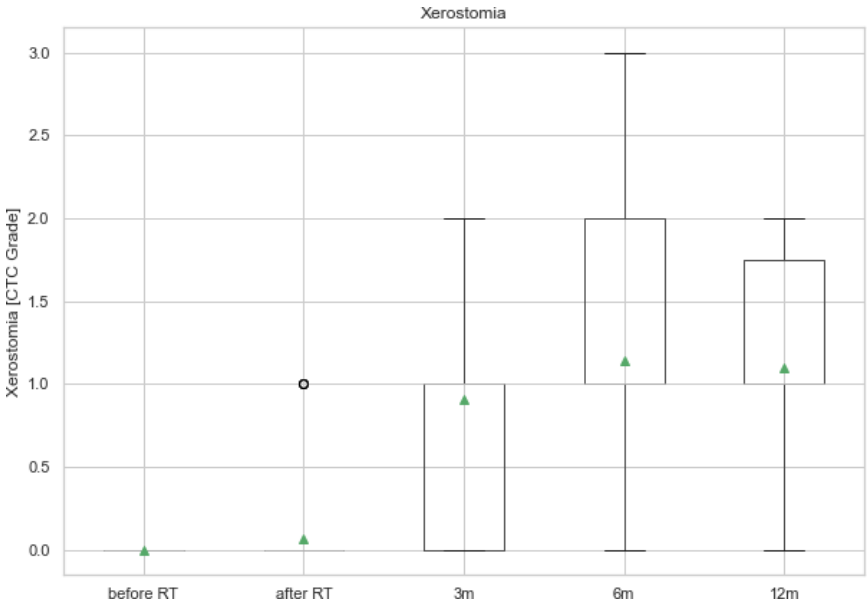


Figure 4.16: Toxicities: Xerostomia vs. time

Tab. 4.24 shows the same data as histograms; the results themselves are listed in Tab. 4.21.

	CTC 0	CTC 1	CTC 2	CTC 3	CTC 4	Average
before RT	44	0	0	0	0	0.00 ± 0.00
after RT	41	3	0	0	0	0.07 ± 0.25
3 months	14	20	10	0	0	0.91 ± 0.74
6 months[4]	6	24	10	1	0	1.15 ± 0.69
12 months[4]	7	24	11	0	0	1.10 ± 0.66

Table 4.21: Xerostomia development with time ($N = 44$)

[4] Excludes missing values

Post-RT xerostomia is not significantly different from pre-RT xerostomia ($p = 0.08$; $t = 1.78$, $df = 43$). Xerostomia at three, six and twelve months after end of RT are each significantly higher than pre-RT ($p < 0.001$ each).

To compare our results to the numbers published in literature - as described in detail in Section 2.2.9 - we calculated the percentage of patients at 12 months or later who reported either xerostomia of grade 1, 2, 3, or 4. We then calculated the average of the published numbers, each of them listed in Table 4.22, and compared them to our percentages.

Table 4.22: Previously published xerostomia data for various time frames. G = Grade of xerostomia (CTCAE)

G0 [%]	**G1 [%]**	**G2 [%]**	**G3 [%]**	**G4 [%]**	**Source**
18	35	20	2	0	published data (avg.)
16	55	25	0	0	UKR (our data)

4.11.2 Dysphagia

Dysphagia ranges from CTC grades zero to four with grade four only just after end of RT. Fig. 4.17 provides an overview about the development of dysphagia averages over time.

Tab. 4.27 shows the same data as histograms for a better overview. Results are listed in Tab. 4.23.

	CTC 0	CTC 1	CTC 2	CTC 3	CTC 4	Average
before RT	40	1	3	0	0	0.16 ± 0.53
after RT	19	3	11	10	1	1.34 ± 1.31
3 months[4]	8	11	12	12	0	1.65 ± 1.09
6 months[4]	9	14	12	6	0	1.37 ± 0.99
12 months[4]	15	15	7	5	0	1.05 ± 1.01

Table 4.23: Dysphagia development with time ($N = 44$)

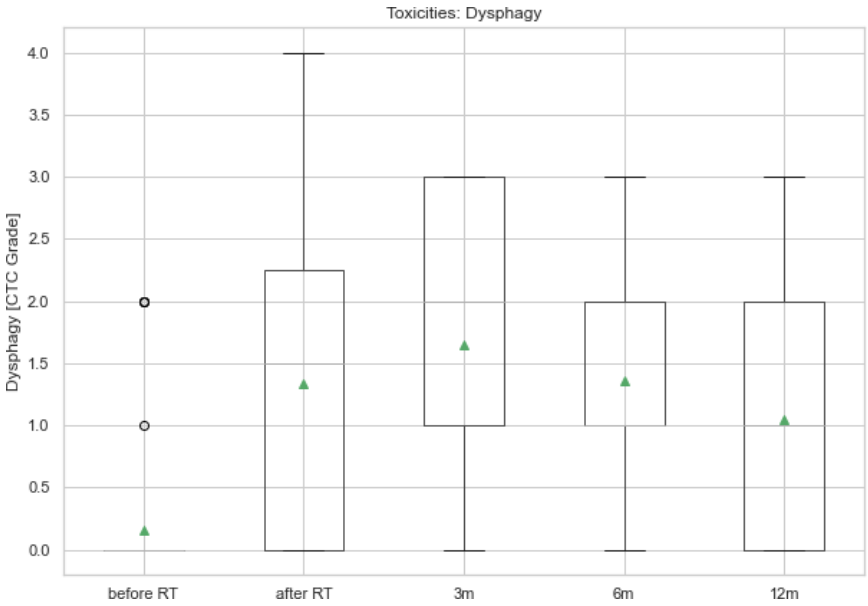


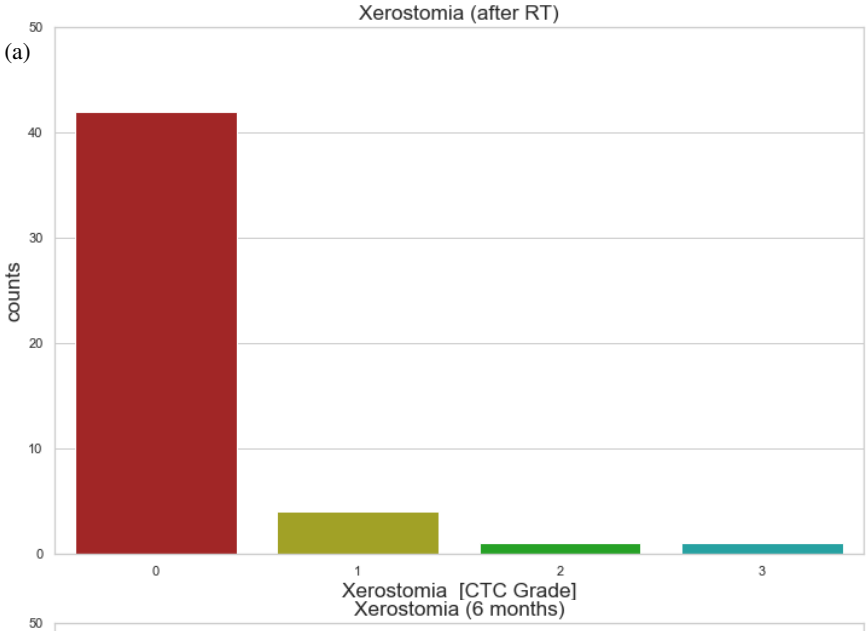
Figure 4.17: Toxicities: Dysphagia vs. time

Post-RT dysphagia is significantly different from pre-RT dysphagia ($p < 0.001$; $t = 1.89$, $df = 41$). Dysphagia at three, six and twelve months after end of RT are also significantly higher than pre-RT ($p < 0.001$ each). Dysphagia at three, six and twelve months after end of RT are not significantly different from dysphagia after RT ($p > 0.05$ each) indicating there is no recovery within this timeframe.

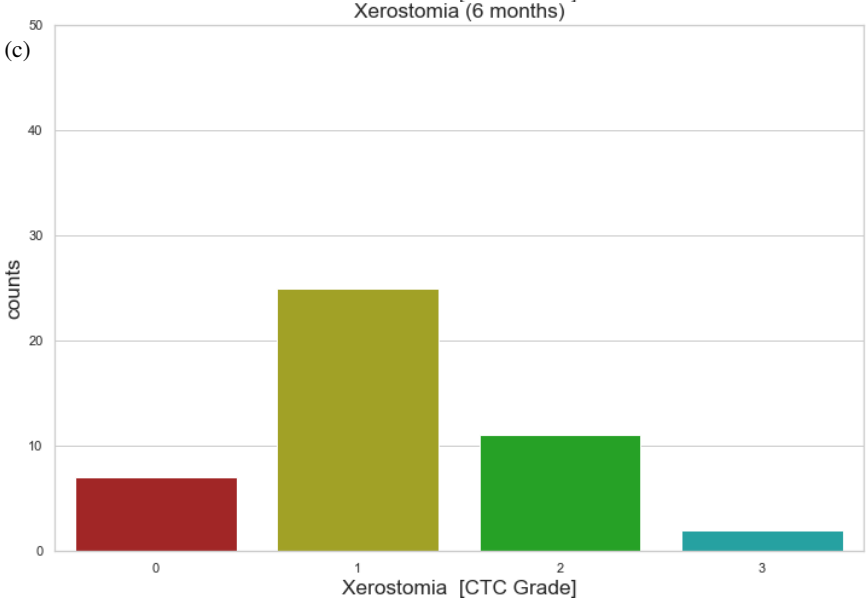
We decided earlier, as explained in detail in Section 2.2.9, that comparison between our results and published numbers is not reasonably possible.

Table 4.24: Toxicities: Xerostomia vs. time

(a)



(c)



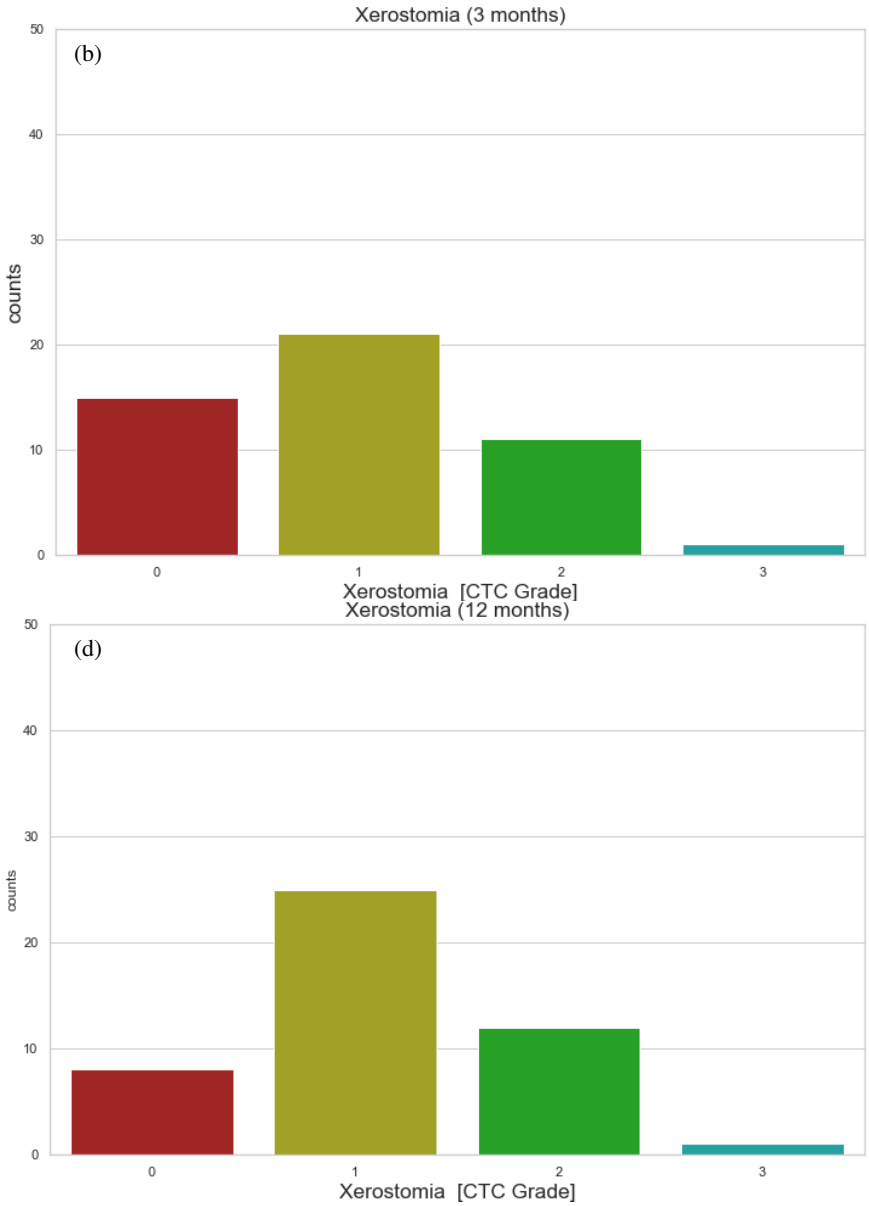
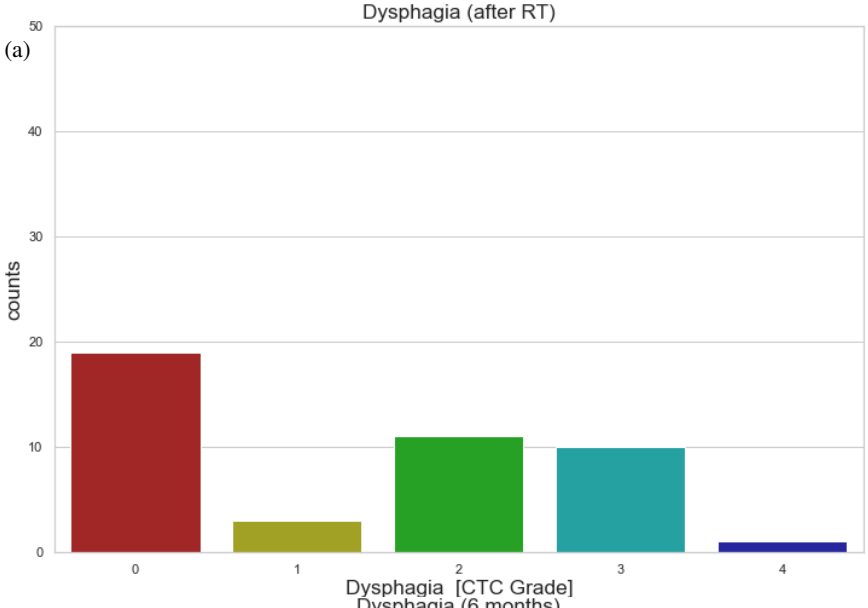
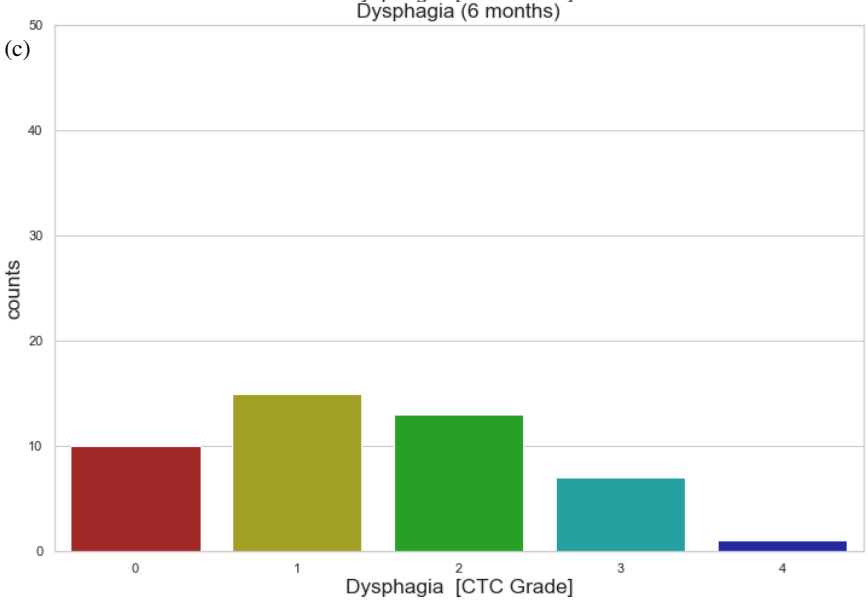

Xerostomia (3 months)
(b)
counts
50
40
30
20
10
0
0
1
2
3
Xerostomia [CTC Grade]
Xerostomia (12 months)
(d)
counts
50
40
30
20
10
0
0
1
2
3
Xerostomia [CTC Grade]

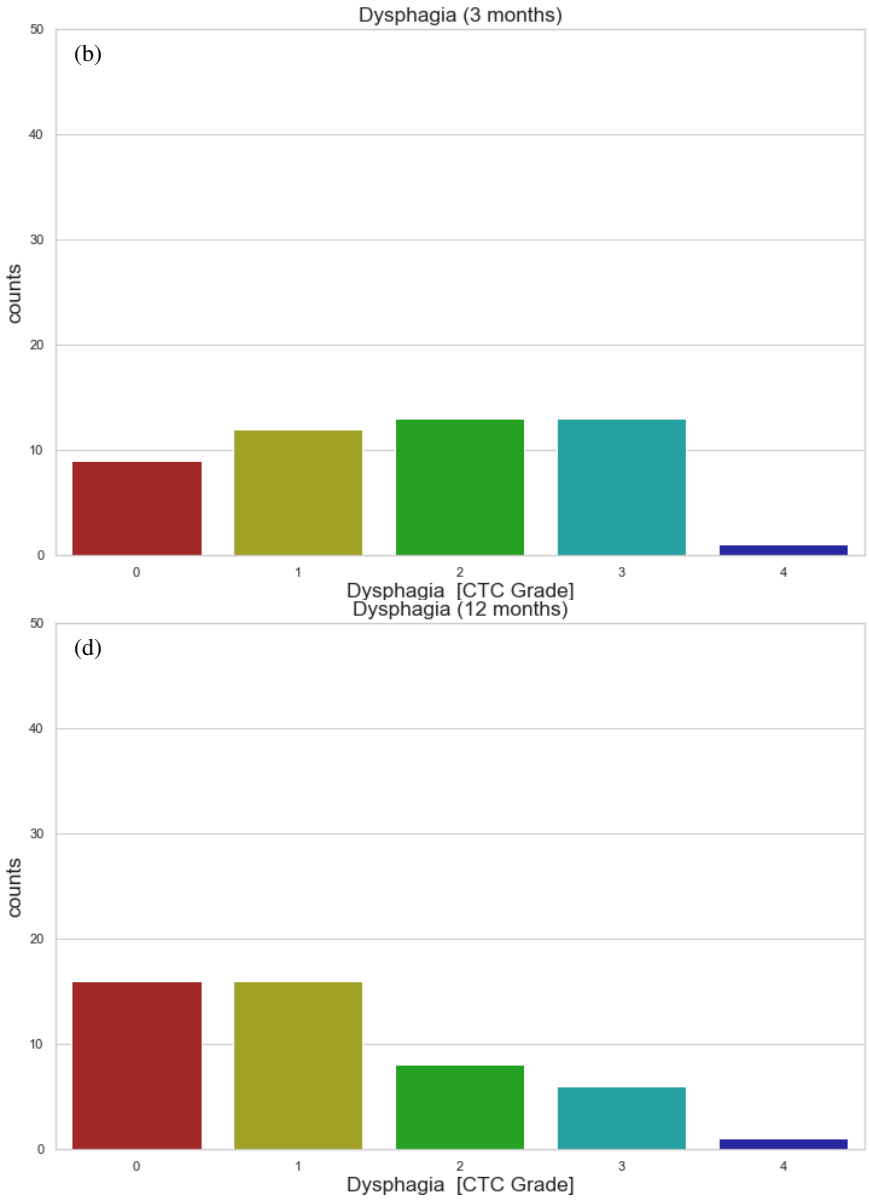
Table 4.27: Toxicities: Dysphagia vs. time

(a)



(c)




Dysphagia (3 months)
(b)
counts
50
40
30
20
10
0
0
1
2
3
4
Dysphagia [CTC Grade]
Dysphagia (12 months)
(d)
counts
50
40
30
20
10
0
0
1
2
3
4
Dysphagia [CTC Grade]

4.12 Objective B.2: Toxicity versus tumor location groups

We analyzed toxicities (xerostomy and dysphagia) in our patient collective to determine if there are differences between the tumor location groups as defined in section 3.7.1.

Xerostomia (see Fig 4.18) was not present before RT in either of the tumor location groups. In the LAR and ORO groups, xerostomia was developed earlier after RT than in the other ones (after approximately three months).

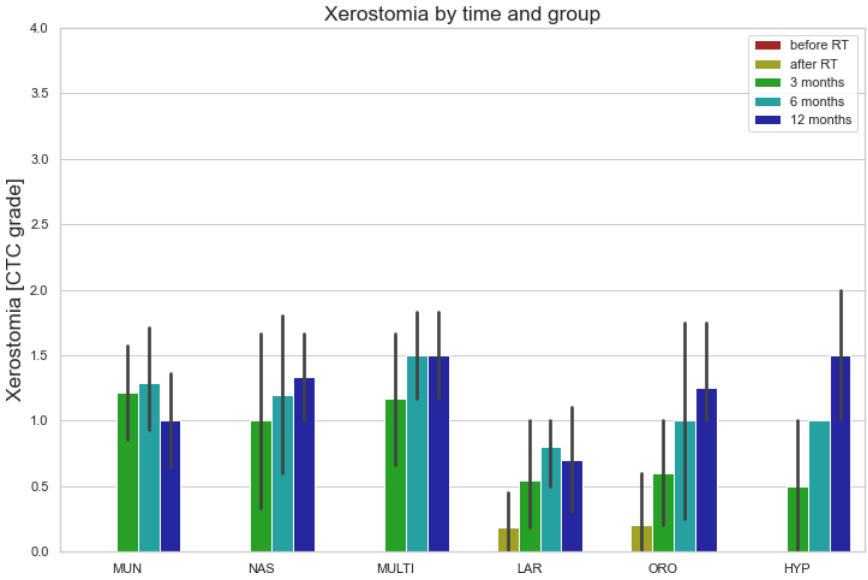


Figure 4.18: Toxicities: Xerostomia vs. time and location groups

Neither ANOVA nor two-sided t-tests showed significant differences between xerostomia group means for any of the timeframes.

Except for the MUN and ORO groups, dysphagia was already present before RT (see Fig 4.19). The MULTI group showed the largest increase in dysphagia within

Group	before RT	after RT	3 months	6 months	12 months
ALL	0.00	0.07	0.90	1.15	1.10
MUN	0.00	0.00	1.21	1.29	1.00
ORO	0.00	0.20	0.60	1.00	1.25
NAS	0.00	0.00	1.00	1.20	1.33
HYP	0.00	0.00	0.50	1.00	1.50
LAR	0.00	0.18	0.55	0.80	0.70
MULTI	0.00	0.00	1.17	1.50	1.50

Table 4.30: Xerostomia by time and tumor location group; ALL: average over all groups.

the first three months after end of RT and decreased afterwards. Dysphagia peaked at 3–6 months in all groups and decreased afterwards.

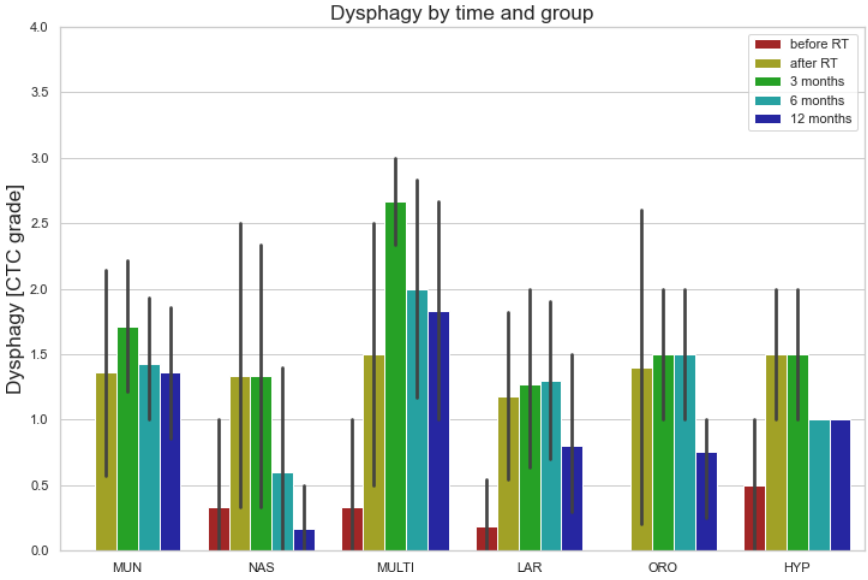


Figure 4.19: Toxicities: dysphagia vs. time and location groups

Group	before RT	after RT	3 months	6 months	12 months
ALL	0.16	1.34	1.65	1.37	1.05
MUN	0.00	1.36	1.71	1.43	1.36
ORO	0.00	1.40	1.50	1.50	0.75
NAS	0.33	1.33	1.33	0.60	**0.17 ****
HYP	0.50	1.50	1.50	1.00	1.00
LAR	0.18	1.18	1.27	1.30	0.80
MULTI	0.33	1.50	**2.67 ****	2.00	1.83

Table 4.31: Dysphagia by time and tumor location group; ALL: average over all groups. Significant difference in means are listed in bold face with two asterisks (**).

ANOVA indicated a tendency towards differences in dysphagia means for the three and twelve months timeframes. Two-sided t-tests confirmed significant differences between group dysphagia means for the NAS group (12 months, $p < 0.01$) and the MULTI group (3 months, $p < 0.01$).

Although there usually is information provided on the tumor location in published studies, it was not specific enough to compile groups similar to ours from them for comparison.

4.13 Objective B.3: Toxicity versus treatment groups

We analyzed toxicities (xerostomy and dysphagia) in our patient collective to determine if there are significant differences between treatment groups (RT vs. RCT).

An overview about our data is presented in Fig. 4.20 (xerostomia) and Fig. 4.21 (dysphagia). Tables 4.32 (xerostomia) and 4.33 (dysphagia) list our results for this objective.

There is no significant difference in xerostomia between the two treatment groups for any timeframe.

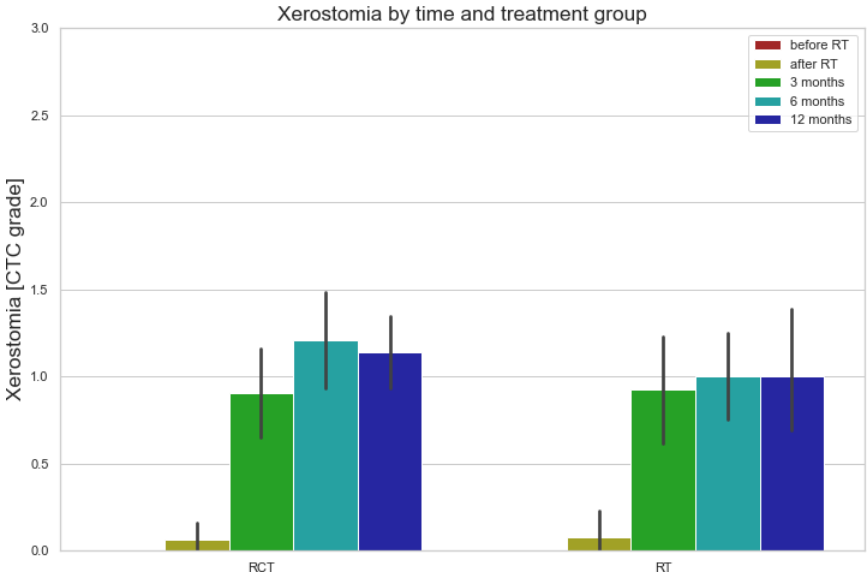


Figure 4.20: Xerostomia vs. time and treatment groups

Group	before RT	after RT	3 months	6 months	12 months
ALL	0.00	0.07	0.90	1.15	1.10
RT	0.00	0.08	0.92	1.00	1.00
RCT	0.00	0.06	0.90	1.21	1.14

Table 4.32: Xerostomia by time and treatment group

ANOVA shows tendencies towards difference for dysphagia means between the RT and RCT groups for the "after RT" timeframe ($p = 0.06$) but no significance.

As mentioned in Section 2.2.11, the data in the majority of the studies about toxicities after radiotherapy (RT) or radiochemotherapy (RCT) shows a lot of variation regarding the ratios between RT and RCT patient numbers. We concluded that comparison of our results to published data regarding this objective is not reasonably possible at this moment.

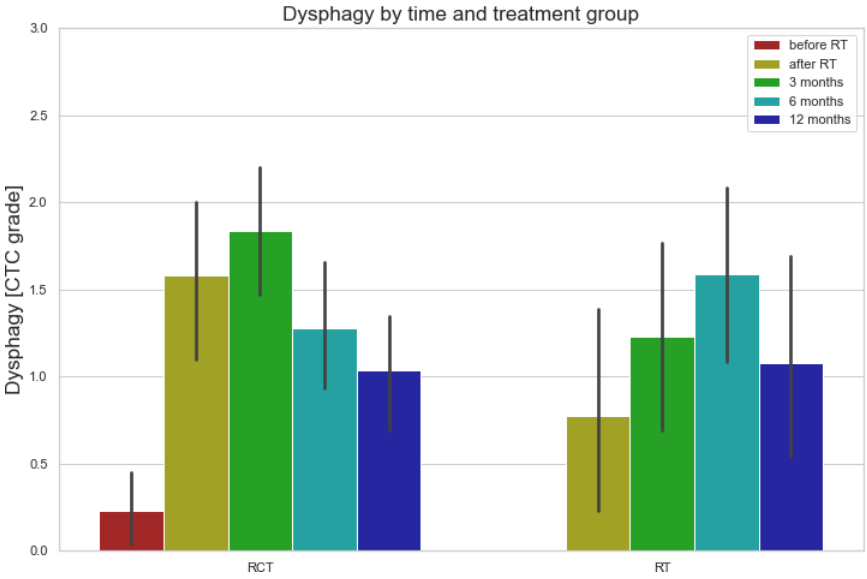


Figure 4.21: Dysphagia vs. time and treatment groups

Group	before RT	after RT	3 months	6 months	12 months
ALL	0.16	1.34	1.65	1.37	1.05
RT	0.00	0.77	1.23	1.58	1.08
RCT	0.23	1.58	1.83	1.28	1.03

Table 4.33: Dysphagia by time and treatment group

4.14 Objective B.4: Toxicity versus gland volume changes

We analyzed toxicities (xerostomy and dysphagia) in our patient collective to determine if there are correlations with the changes in gland volumes described above.

Table 4.35 below shows an overview for xerostomia versus gland volume changes for all timeframes, the corresponding results are listed in Tab. 4.34.

	dV (CTC 0)	*dV* (CTC 1)	*dV* (CTC 2)	*dV* (CTC 3))
after RT	0.76	0.83	-	-
3 months	0.80	0.80	0.63	-
6 months	0.80	0.82	0.63	0.71
12 months	0.94	0.78	0.65	-

Table 4.34: Xerostomia vs. gland volume changes with time. All values are given in ratios of gland volume change dV = V(after)/V(before).

No significant correlations between xerostomia and gland volume changes could be identified.

Table 4.39 below shows an overview for dysphagia versus gland volume changes for all timeframes, the corresponding results are listed in Tab. 4.38.

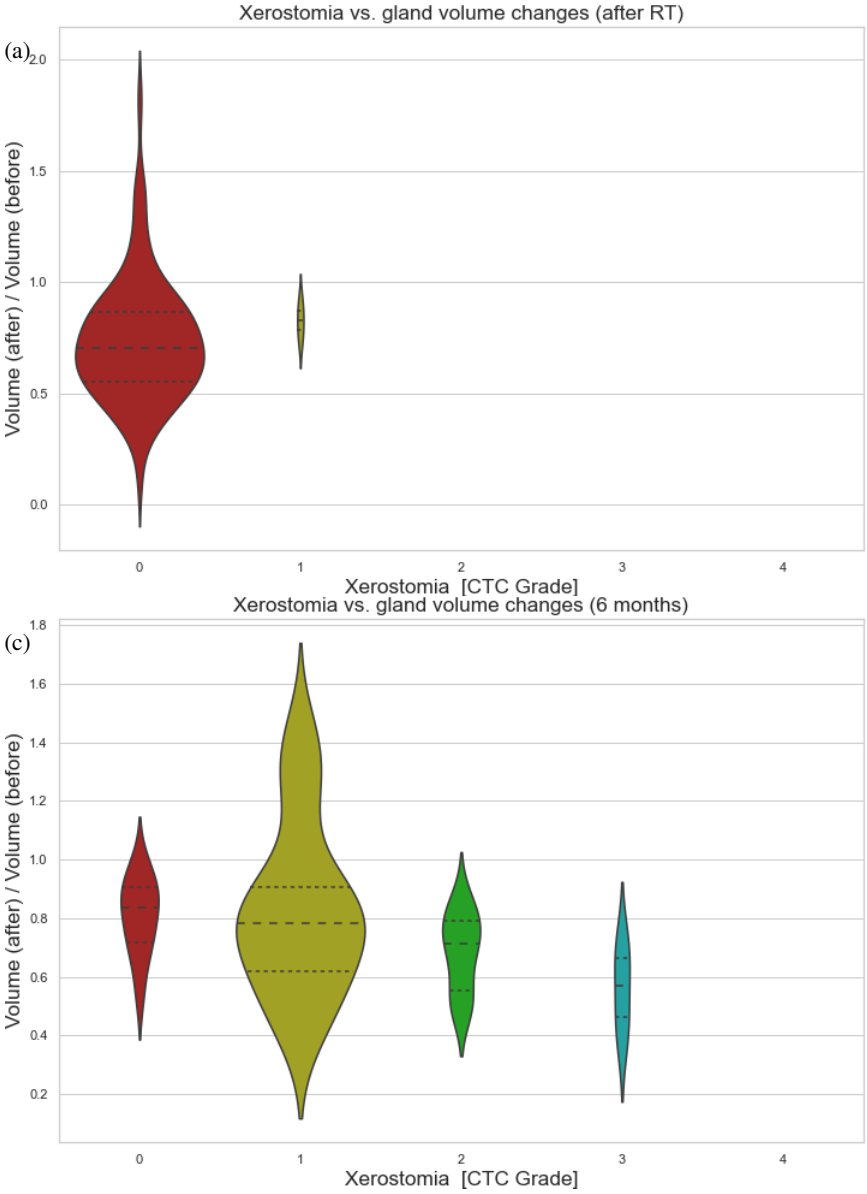
	dV (CTC 0)	*dV* (CTC 1)	*dV* (CTC 2)	*dV* (CTC 3)	*dV* (CTC 4)
before RT	0.76	0.80	0.72	-	-
after RT	0.85	0.80	0.65	0.84	0.82
3 months	0.88	0.71	0.83	0.63	-
6 months	0.83	0.78	0.82	0.72	-
12 months	0.62	0.88	0.84	0.74	-

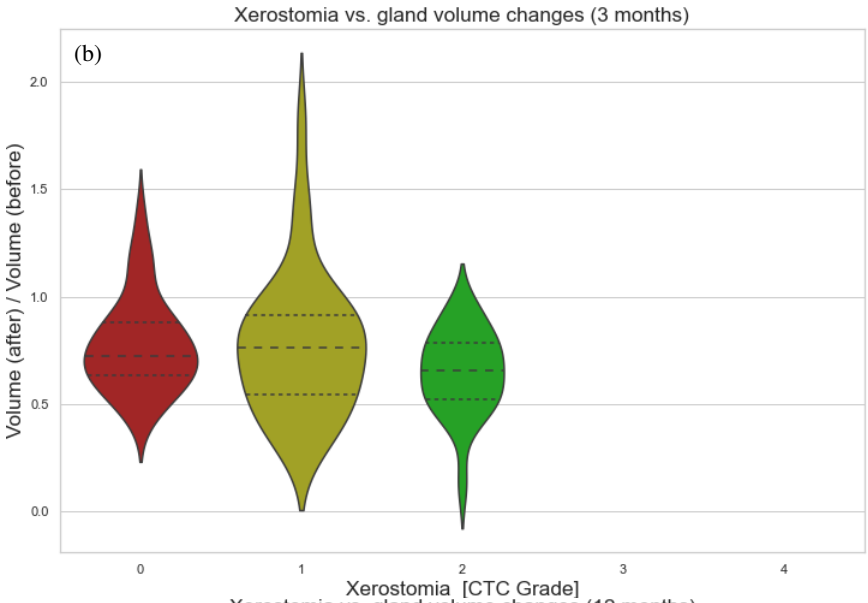
Table 4.38: Dysphagia vs. gland volume changes with time. All values are given in ratios of gland volume change dV = V(after)/V(before).

No significant correlations between dysphagia and gland volume changes could be identified.

We could not find sufficient data for comparison.

Table 4.35: Xerostomia versus gland volume changes with time




Xerostomia vs. gland volume changes (3 months)
(b)
Volume (after) / Volume (before)
2.0
1.5
1.0
0.5
0.0
0
1
2
3
4
Xerostomia [CTC Grade]

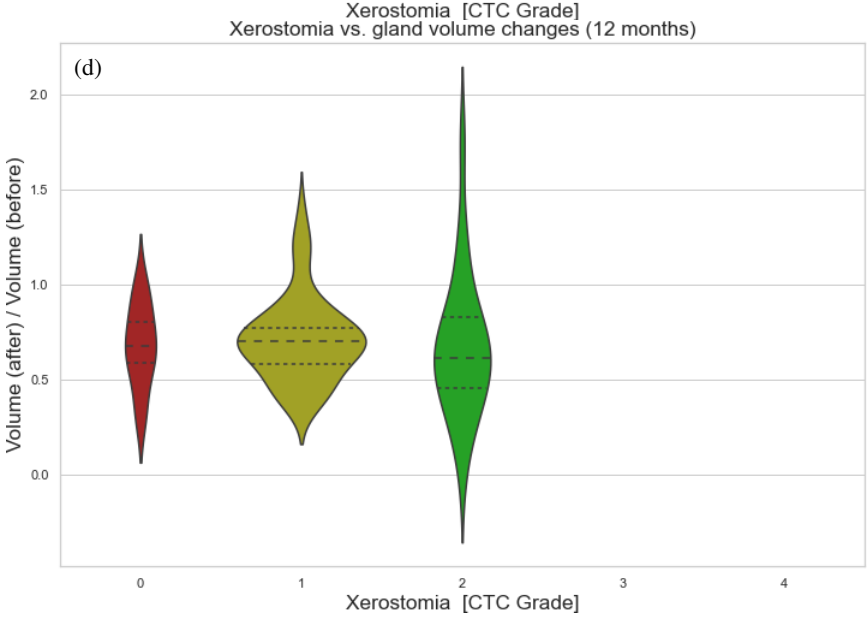
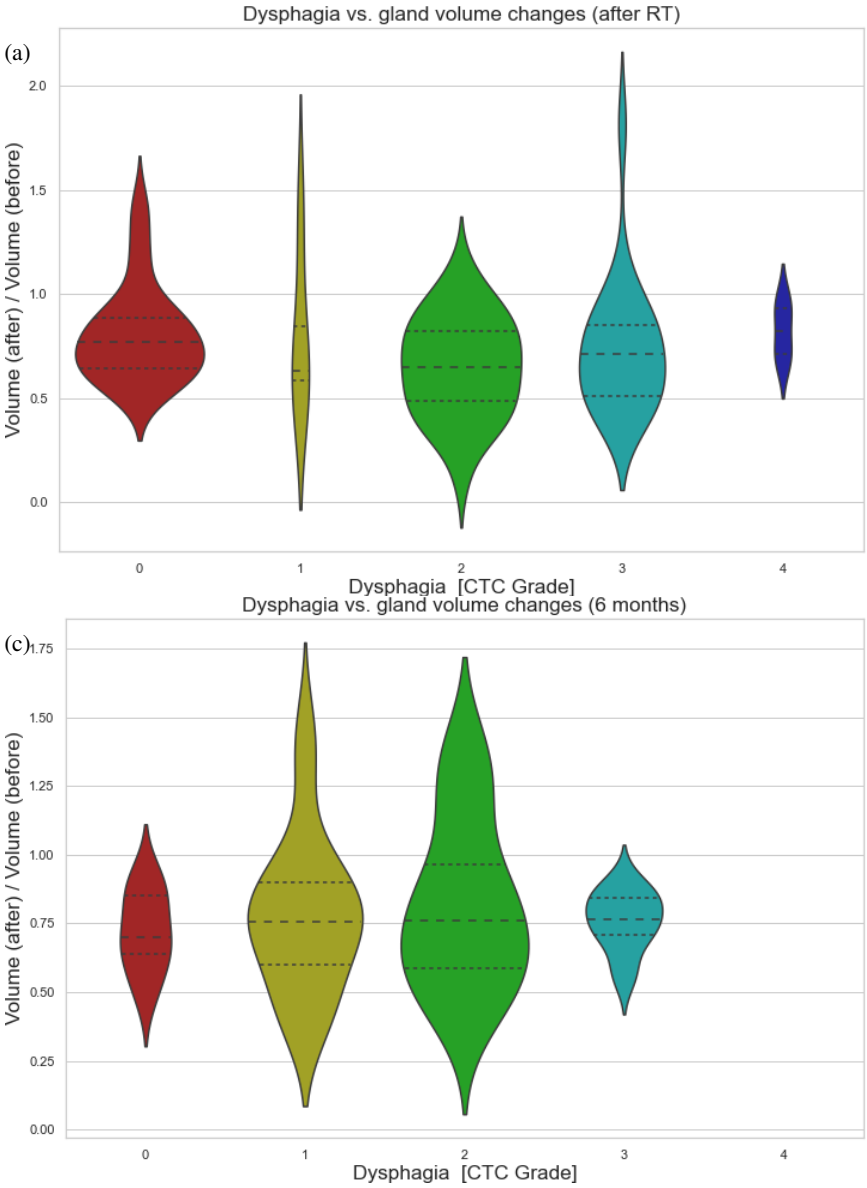
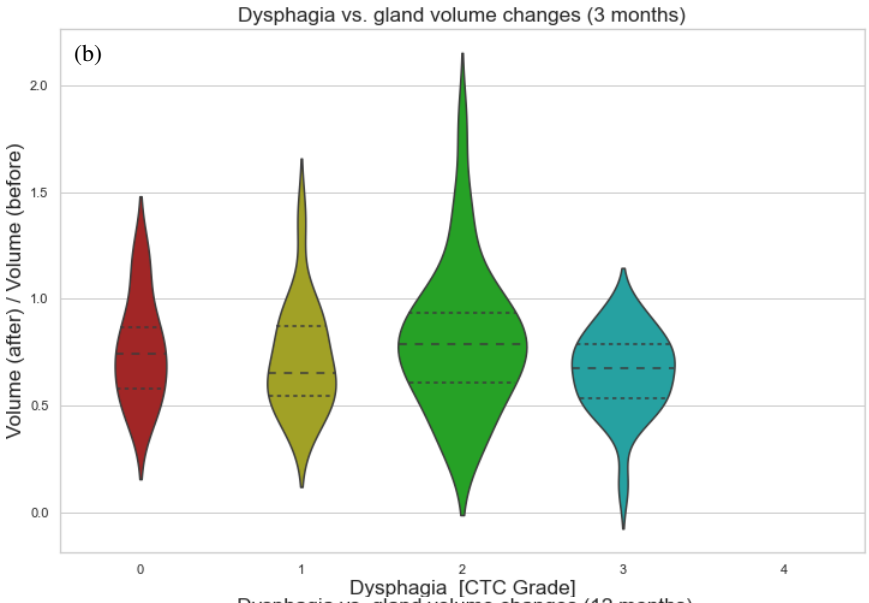
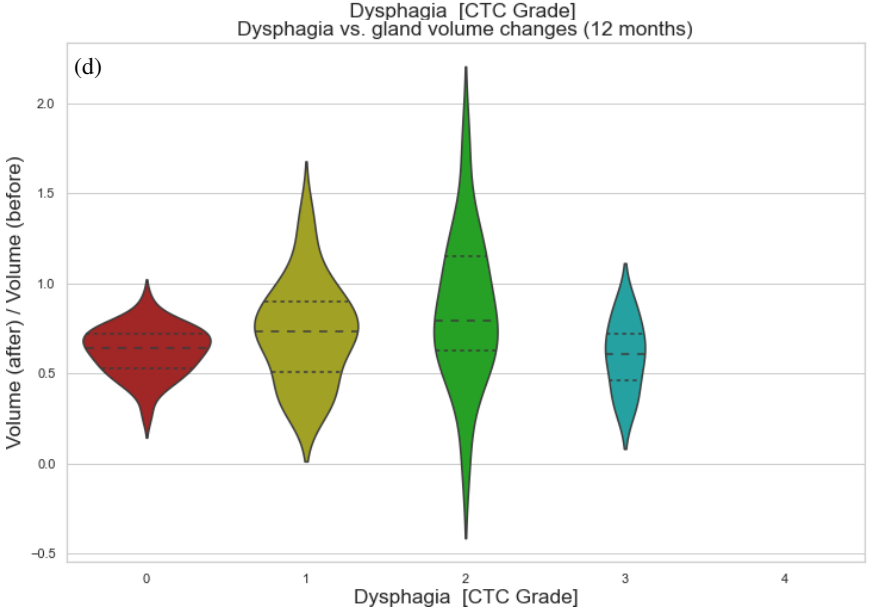

Xerostomia vs. gland volume changes (12 months)
(d)
Volume (after) / Volume (before)
2.0
1.5
1.0
0.5
0.0
0
1
2
3
4
Xerostomia [CTC Grade]

Table 4.39: Dysphagia versus gland volume changes with time




Dysphagia vs. gland volume changes (3 months)
(b)
Volume (after) / Volume (before)
2.0
1.5
1.0
0.5
0.0
0
1
2
3
4
Dysphagia [CTC Grade]


Dysphagia vs. gland volume changes (12 months)
(d)
Volume (after) / Volume (before)
2.0
1.5
1.0
0.5
0.0
−0.5
0
1
2
3
4
Dysphagia [CTC Grade]

4.15 Objective B.5: Toxicity versus received doses

We analyzed toxicities (xerostomy, and dysphagia) in our patient collective to determine if there are significant correlations with the received doses.

Looking at data from both parotids as well as from both submandibular glands after RT and after 3 (6, 12) months, we see a distribution of received mean dose with two peaks at approximately 35 Gy and 70 Gy, respectively (as shown in Fig.4.22 as an example). This can be explained by the fact that dose is distributed differently between parotids (which are regions of interest (ROI) in treatment planning) and submandibulars (which are not ROI's).

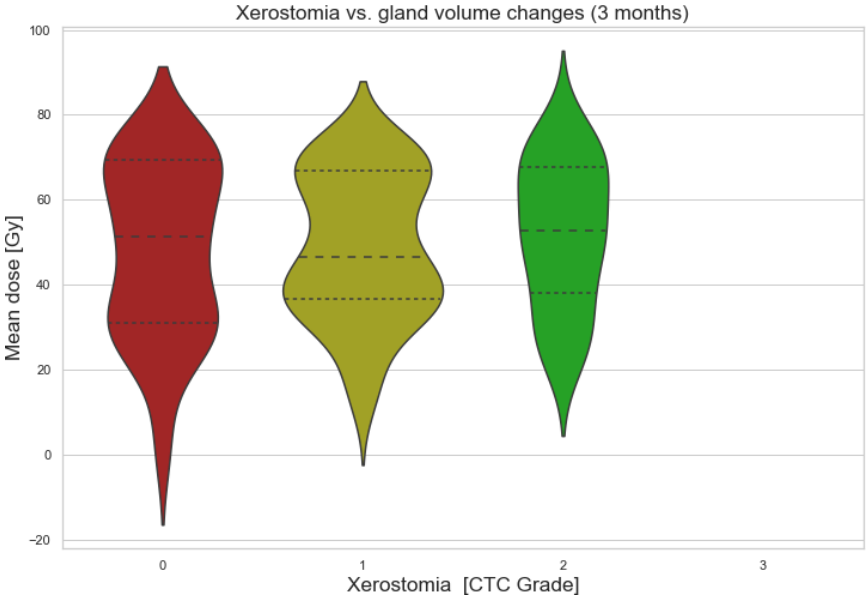


Figure 4.22: Xerostomia vs. received mean dose (3 months)

To avoid these artefacts we decided to split the data into two gland groups - one for the left and right parotids, and another one for the left and right submandibular gland.

The results for the parotid glands are shown in Tab. 4.42 (xerostomia) and Tab.4.46 (dysphagia) below.

Starting at approximately three months after end of RT the grades of xerostomia are clearly associated with the received mean dose - the more dose the parotids received, the higher the grade of xerostomia.

	CTC 0 [Gy]	CTC 1 [Gy]	CTC 2 [Gy]	CTC 3 [Gy]
after RT	38.08	31.36	-	-
3 months	35.58	38.54	40.65	-
6 months	33.41	37.69	43.95	55.82
12 months	26.87	39.50	39.29	-

Table 4.45: Mean parotid gland dose with time by CTC grade xerostomia

	CTC 0 [Gy]	CTC 1 [Gy]	CTC 2 [Gy]	CTC 3 [Gy]	CTC 4 [Gy]
after RT	37.23	38.01	41.11	36.65	35.23
3 months	32.21	37.02	37.30	42.75	-
6 months	38.72	33.43	40.77	49.09	-
12 months	34.50	35.69	39.46	47.81	-

Table 4.49: Mean parotid gland dose with time by CTC grade dysphagia

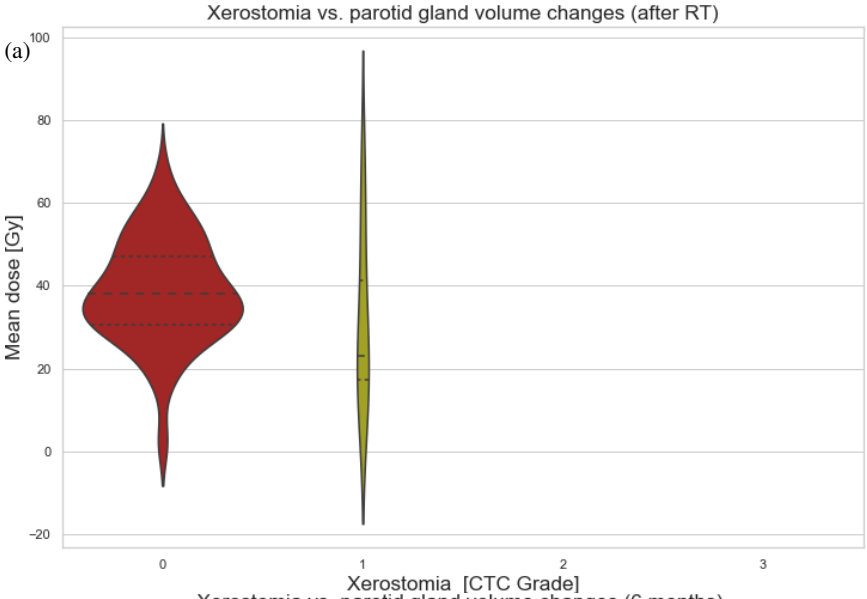
The results for the submandibular glands are shown in Tab. 4.50 (xerostomia) and 4.53 (dysphagia) below.

There is no evidence for correlation of mean gland dose for the submandibular glands with neither xerostomia nor dysphagia.

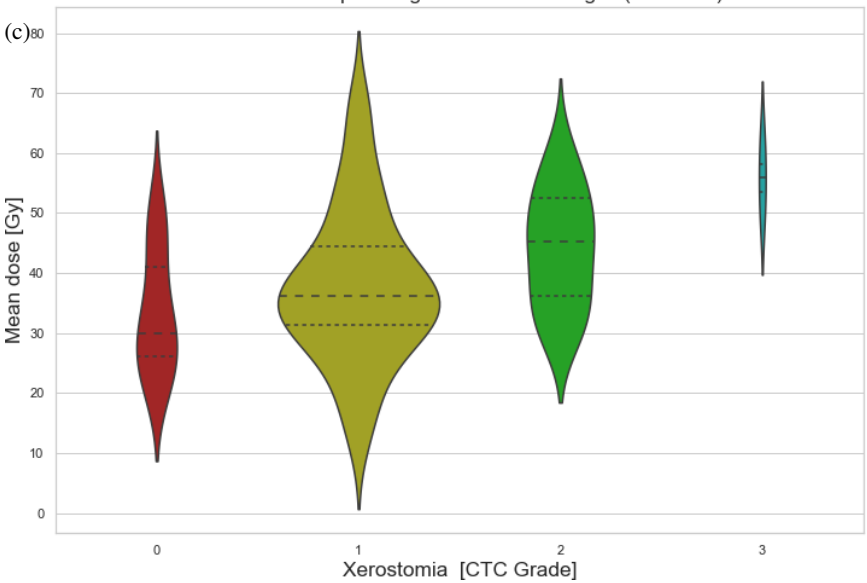
For reasons explained in detail in Section 2.2.13 earlier, comparison of previously published data to our results is not reasonably possible.

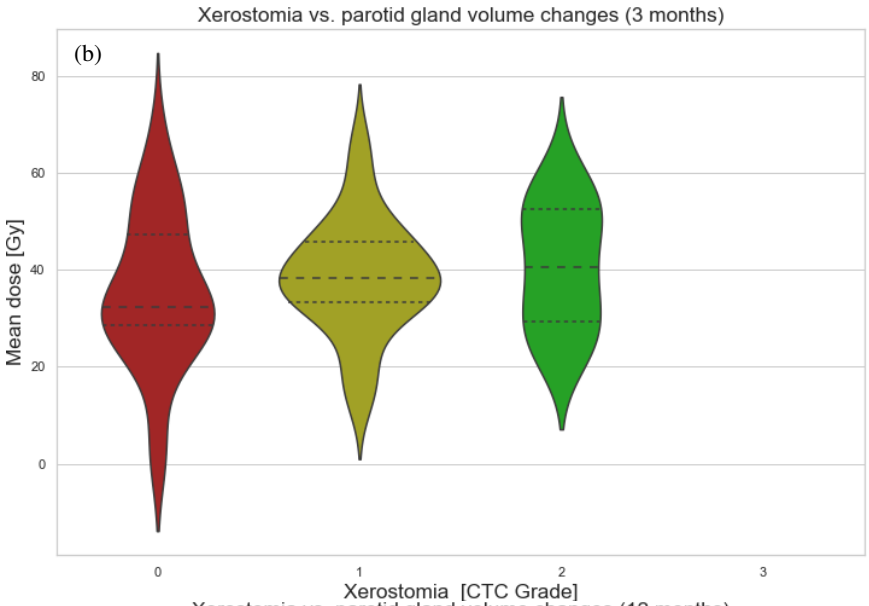
Table 4.42: Xerostomia vs. received parotid glands mean dose with time

(a)



(c)




Xerostomia vs. parotid gland volume changes (3 months)
(b)
Mean dose [Gy]
0
20
40
60
80
0
1
2
3
Xerostomia [CTC Grade]

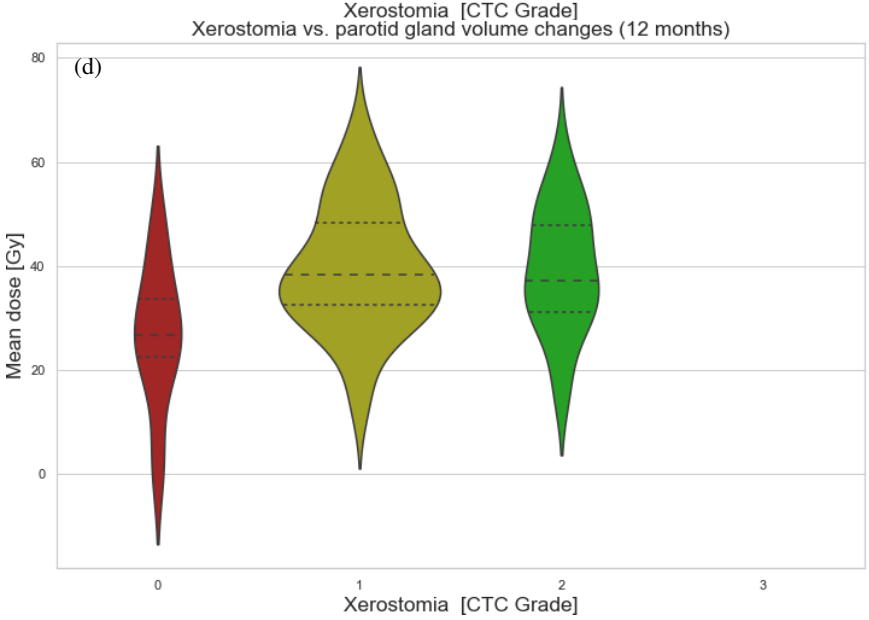
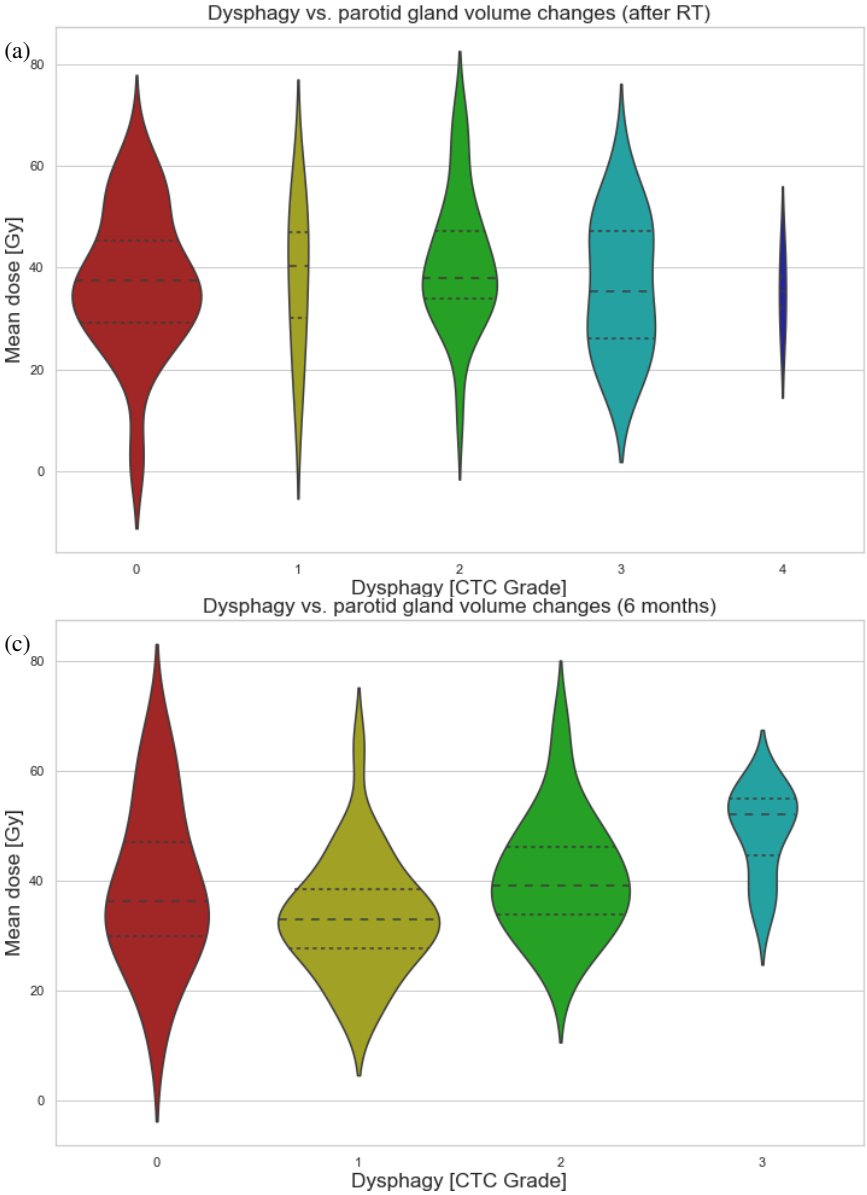
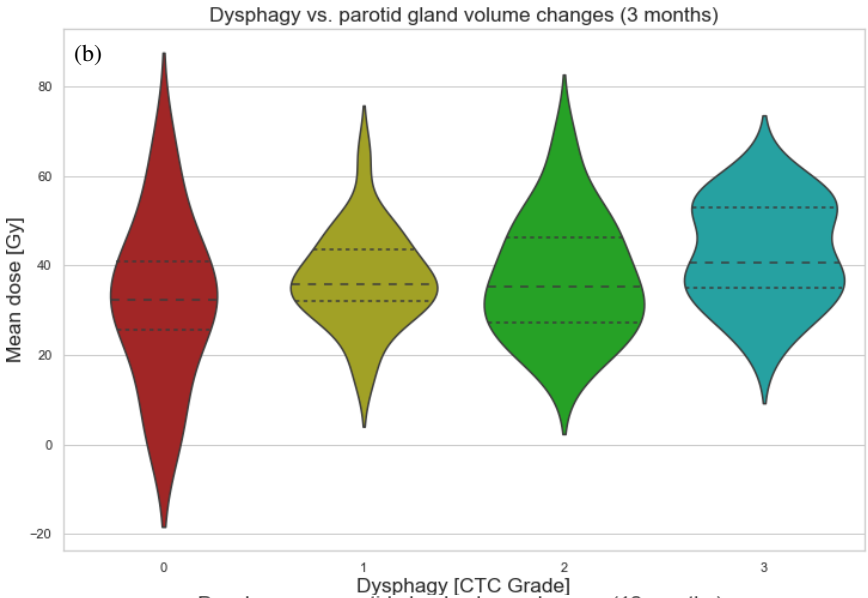

Xerostomia vs. parotid gland volume changes (12 months)
(d)
Mean dose [Gy]
0
20
40
60
80
0
1
2
3
Xerostomia [CTC Grade]

Table 4.46: Dysphagia vs. received parotid glands mean dose with time




Dysphagy vs. parotid gland volume changes (3 months)
(b)
Mean dose [Gy]
80
60
40
20
0
−20
0
1
2
3
Dysphagy [CTC Grade]

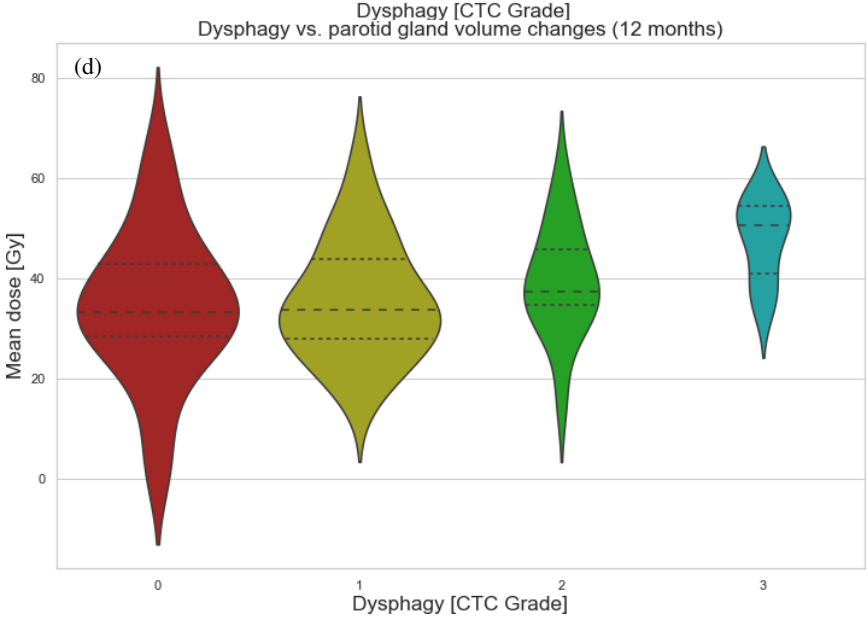
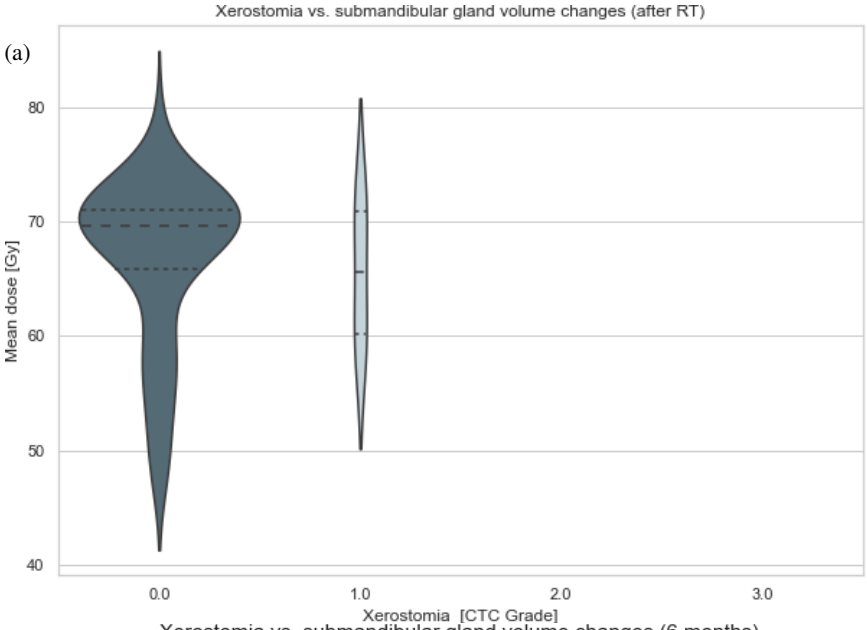
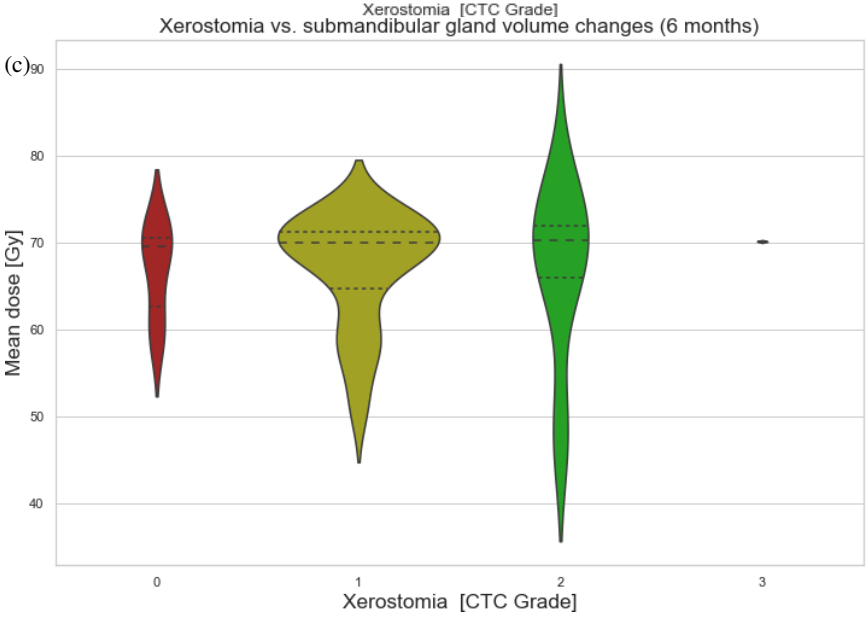
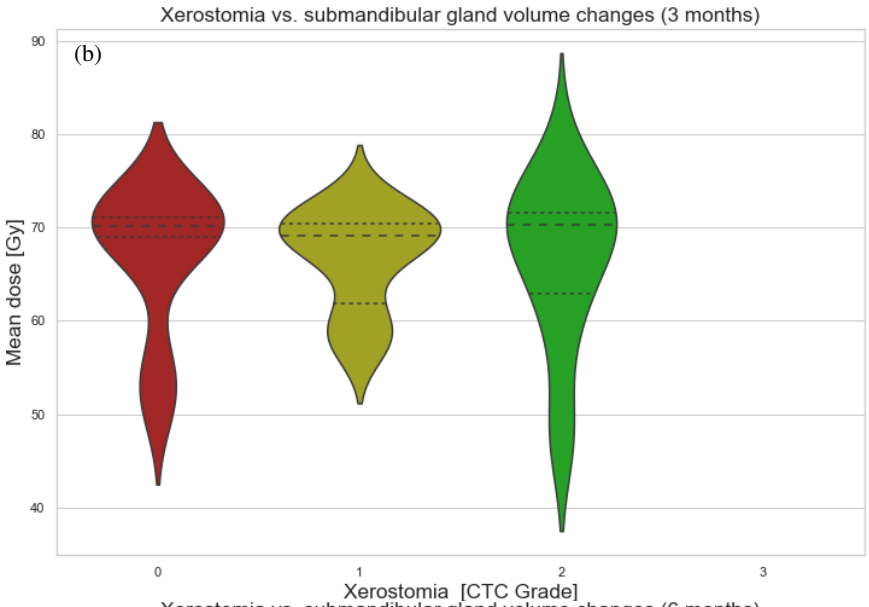

Dysphagy vs. parotid gland volume changes (12 months)
(d)
Mean dose [Gy]
80
60
40
20
0
0
1
2
3
Dysphagy [CTC Grade]

Table 4.50: Xerostomia vs. received submandibular glands mean dose with time






Xerostomia vs. submandibular gland volume changes (3 months)
(b)
Mean dose [Gy]
90
80
70
60
50
40
0
1
2
3
Xerostomia [CTC Grade]

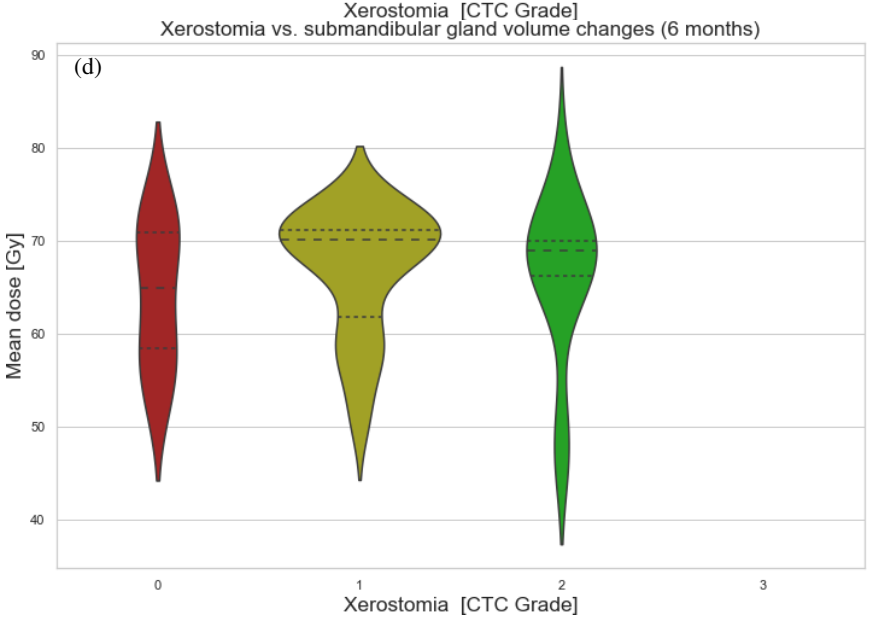
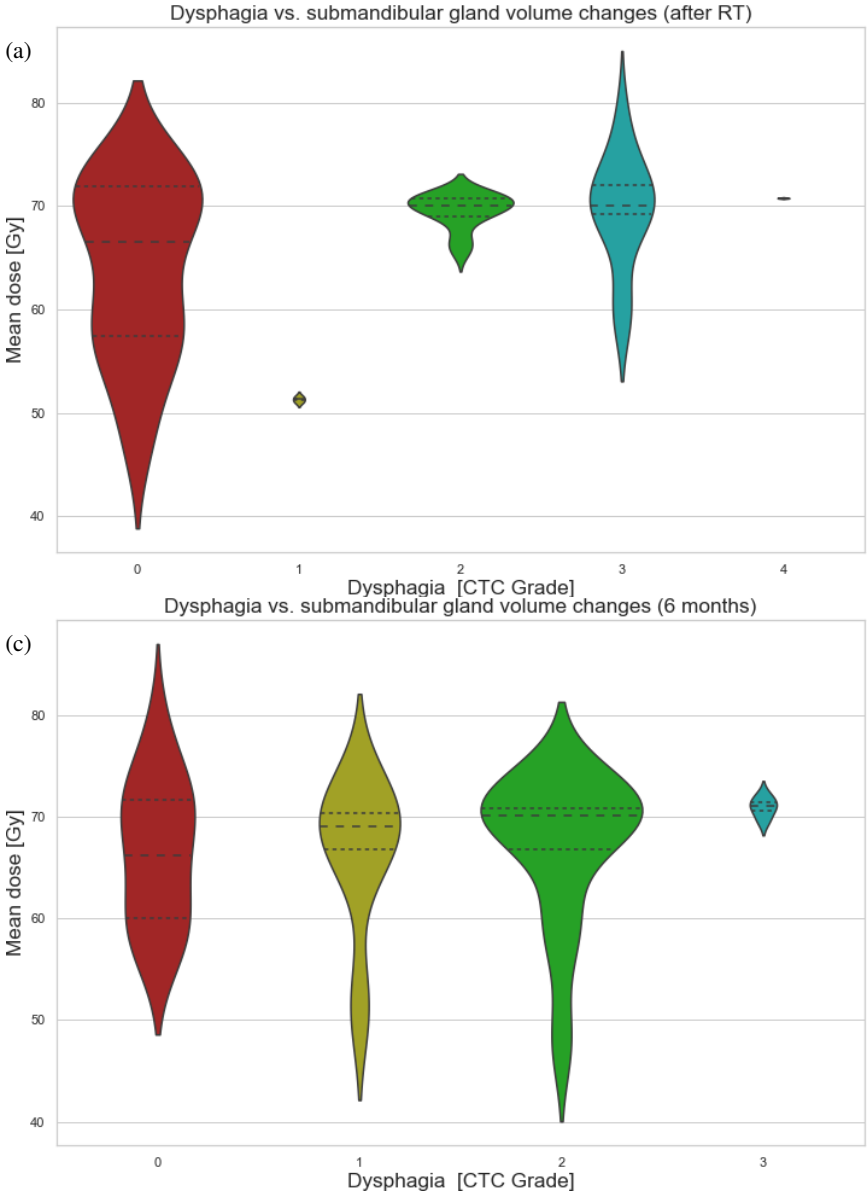
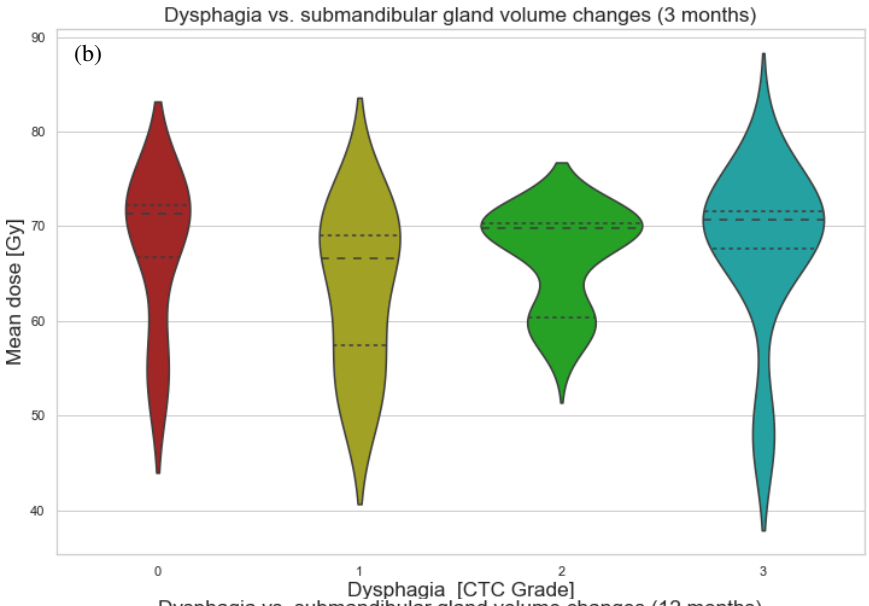
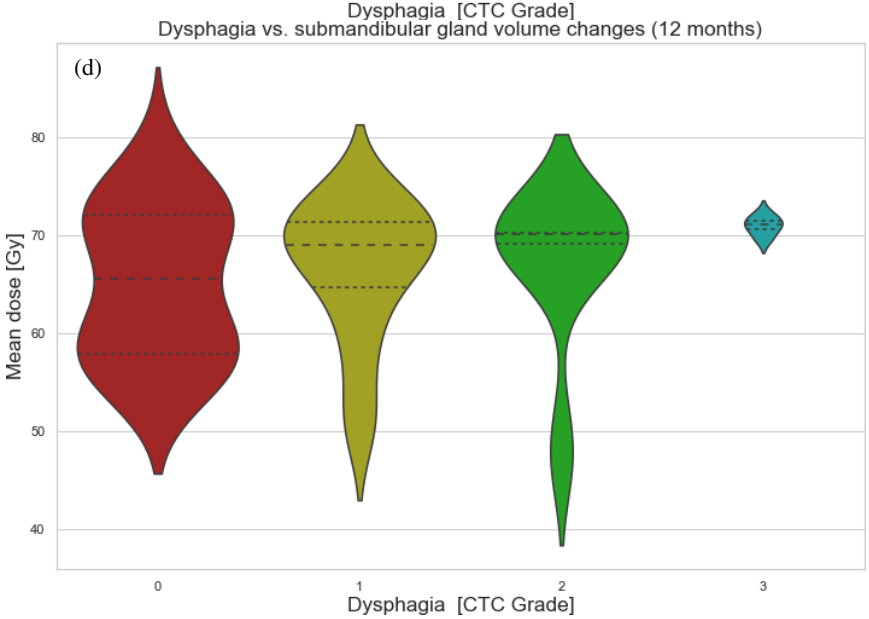

Xerostomia vs. submandibular gland volume changes (6 months)
(d)
Mean dose [Gy]
90
80
70
60
50
40
0
1
2
3
Xerostomia [CTC Grade]

Table 4.53: Dysphagia vs. received submandibular glands mean dose with time




Dysphagia vs. submandibular gland volume changes (3 months)
(b)
Mean dose [Gy]
90
80
70
60
50
40
0
1
2
3
Dysphagia [CTC Grade]


Dysphagia vs. submandibular gland volume changes (12 months)
(d)
Mean dose [Gy]
80
70
60
50
40
0
1
2
3
Dysphagia [CTC Grade]

Chapter 5

Discussion

5.1 Key Results

5.1.1 Volume effects

Gland volumes decreased by an average of 34% (parotids) and 18% (submandibulars) after radiotherapy (details can be found in Section 4.5). The values for both the parotid and the submandibular glands are in good accordance with the values published in literature: For the parotid gland, reported volume loss was 1between 17% and 38% (mean: 28%). [5, 33, 35–40, 42, 43, 45–51].

A graphical overview of these results compared to ours are shown in Figure 4.6 (PG) and Figure 4.7 (SMG).

Gland volumes are not recovering within 36 months after end of radiotherapy (for details please see Section 4.6). As salivary gland tissue is damaged by ionizing radiation and not recovering easily this is not surprising. Once the damage is done, loss of organ function seems inevitable and irreversible; this result adds more evidence for this assumption. This result is in good accordance with data published in literature; none of the recent publications show complete recovery to pre-treatment gland volumes.[12, 16, 52, 53]

A weak correlation was found between gland volume changes and mean gland doses (Section 4.7). We think the correlation might be stronger with a larger patient collective as the underlying common theory of function loss by volume loss induced by damage of ionizing radiation strongly suggests so.

One tumor location group (tumors of the nasopharynx, NAS) received significantly lower doses than the other groups (Section 4.9). This is probably a non-significant

effect of our small patient collective - we did not expect this result when taking into account the primary target volumes with respect to the anatomy of the salivary glands which was our assumption to be the largest factor.

There was no difference between tumor location groups (Section 4.9) or treatment (RT vs. RCT, Section 4.10) or with respect to changes in gland volume. Comparison with published data was not feasible for both. No difference between treatment groups (RT vs. RCT) adds evidence to the assumption that the chemotherapy used at UKR for this specific kind of tumors is not specifically toxic to the salivary glands, at least with behold to changes of gland volume. No difference between tumor location groups is questionable when looking at primary target volumes near salivary glands or with larger distance to them, for example the NAS and HYP groups could be seen as possibly different in their gland volume changes. This might be a consequence of our small patient collective.

5.1.2 Xerostomia

Post-RT xerostomia is not significantly different from pre-RT xerostomia (Section 4.11.1). Xerostomia at three, six and twelve months after end of RT are each significantly higher than pre-RT (Section 4.11.1). This is in good accordance with both results published in recent literature (for details see Section 2.2.9 and 4.11) and with the results presented above, especially in Section 4.5.

Xerostomia was not present before RT in either of the tumor location groups (Section 4.12). In the LAR and ORO groups xerostomia was developed earlier (after RT) than in the other ones (after approximately three months, Section 4.12). We currently don't know whether this is an unexpected result with an underlying cause or an effect by the small patient collective. We added this problem to the list of topics for further studies discussed below.

There is no significant difference in xerostomia between the two treatment groups (RT vs. RCT) for any timeframe (Section 4.13).

No significant correlations between xerostomia and gland volume changes could be identified (Section 4.14). There are two possible explanations: First, our patient collective might be too small to show significant correlations. Secondly, gland volume changes could not the only cause of xerostomia after radiotherapy of head and neck tumors. The latter is discussed in literature as outlined in 2.2.12.

Starting at approximately three months after end of RT the grades of xerostomia are clearly associated with the received mean parotid gland dose - the more dose the parotids received, the higher the grade of xerostomia. There is no evidence for correlation of mean gland dose for the submandibular glands with xerostomia (Section 4.15) - again, this is most probably caused by our small patient collective as discussed earlier.

5.1.3 Dysphagia

Post-RT dysphagia is significantly different from pre-RT dysphagia. Dysphagia at three, six and twelve months after end of RT are also significantly higher than pre-RT. Dysphagia at three, six and twelve months after end of RT are not significantly different from dysphagia after RT, indicating there is no recovery within this timeframe. Details are provided in Section 4.11.2. Dysphagia has an earlier onset than xerostomia which is likely linked to inflammation in the oropharyngeal mucosa which is reflected nicely in our results.

We found significant differences between tumor location group dysphagia means for the NAS group (12 months) and the MULTI group (3 months). For details please see Section 4.12. This effects are subject to further discussion as discussed below.

Except for the MUN and ORO groups, dysphagia was already present before RT. The MULTI group showed the largest increase in dysphagia within the first three months after end of RT and decreased afterwards. Dysphagia peaked at 3–6 months in all groups and decreased afterwards as expected.

Also, no significant correlations between dysphagia and gland volume changes could be identified (Section 4.14. This is in accordance of our assumption that dysphagia is mostly caused by mucositis as a direct result or direct impact from radiotherapy, not due to effects caused by gland volume changes.

There is no evidence for correlation of mean gland dose for the submandibular glands with dysphagia (Section 4.15).

5.2 Limitations & Generalisability

The most obvious limitation might be our relatively small patient collective of only 44 patients with full data points available.

Coming from a collective of originally 269 patients (for details please see Section 4.1) the basis seems solid, though: We were able to not only reproduce gland volume changes in parotid glands as described in Section 4.5, but also set measures for the submandibular glands which are represented rather poorly in recent research.

Even though we only had 44 patients in our data collective we had more data on the development of both gland volume changes and toxicities: We had access to data in our collective for both areas of research for up to 36 months after end of radiotherapy (see 3.7.2 for details on the time scale). Publications with data for further than 12 months after end of radiotherapy are rare, so we are quite happy to present new and hopefully useful data in this thesis.

5.3 Further Studies

As mentioned above, xerostomia developed earlier after radiotherapy in the LAR and ORO groups than in the other ones (Section 4.12). We recommend repeating this experiment with a larger patient collective to answer the question whether this is a solid effect or rather an artefact.

We found significant differences between tumor location group dysphagia means for the NAS group (12 months) and the MULTI group (3 months). We recommend further studies with a larger patient collective.

There are two interesting questions arising as a conclusion of the changes in gland volume we showed in this thesis:

- Are there significant changes in the anatomy with respect to the salivary glands with effects on the regions of interest?
- As a result of these eventual changes in anatomy, is there an option for re-planning during radiotherapy to further minimize the side effects and toxicities?

Answering these two questions could eventually lead to increase in the quality of life for patients with head and neck tumors treated with radio- or radiochemotherapy.

In memoriam Stephen John Moore (1961–2018)

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