Longitudinal Assessment of Parotid Function in Patients Receiving Tomotherapy for Head-and-Neck Cancer

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Background and Purpose: Conventional radiotherapy is associated with high doses to the salivary glands which causes xerostomia and adverse effects on quality of life. The study aims to investigate the potential of helical tomotherapy (Hi-Art Tomotherapy®) to preserve parotid function in head-and-neck cancer patients.
Patients and Methods: Seven consecutive patients treated with helical tomotherapy at the UZ Brussel, Belgium, were included. During planning, priority was attributed to planning target volume (PTV) coverage: ≥ 95% of the dose must be delivered to ≥ 95% of the PTV. Elective nodal regions received 54 Gy (1.8 Gy/fraction). A dose of 70.5 Gy (2.35 Gy/fraction) was prescribed to the primary tumor and pathologic lymph nodes = simultaneous integrated boost scheme. If possible, the mean parotid dose was kept below 26 Gy. Salivary gland function was assessed by technetium scintigraphy.
Results: There was a significant dose-response relationship between mean parotid dose and functional recuperation. If the mean dose was kept < 31 Gy, a recuperation of 75% can be expected at 12 months. The authors equally observed a significant correlation between salivary excretion (SE) and the percentage of parotid gland receiving a dose < 26 Gy (V_{26}%). In order to preserve 75% of SE, 46% of the parotid volume should receive a dose < 26 Gy.
Conclusion: With the use of helical tomography the parotid gland function can largely be preserved since the mean dose to the entire gland as well as glandular volume receiving > 26 Gy can be reduced.

Key Words: Head-and-neck cancer · Helical tomotherapy · Parotid sparing

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Longitudinale Abschätzung der Speicheldrüsenfunktion bei Patienten mit helikaler Tomotherapie von Kopf-Hals-Tumoren

Hintergrund und Ziel: Die konventionelle Strahlentherapie zur Behandlung von Kopf-Hals-Tumoren steht häufig im Zusammenhang mit hohen Dosisbelastungen der Speicheldrüsen. Dies verursacht Xerostomie, welche eine Beeinträchtigung der Lebensqualität zur Folge hat. Das Ziel dieser Studie ist die Untersuchung eines möglichen Vorteils helikaler Tomotherapie für die Funktionserhaltung der Ohrspeicheldrüsen.
Patienten und Methodik: Eingeschlossen wurden sieben aufeinanderfolgende Patienten mit einer Nachbeobachtungszeit von 12 Monaten, die am Universitätsklinikum Brüssel (UZ Brussel), Belgien, eine helikale Tomotherapie (Hi-Art Tomotherapy®) erhielten. Bei der Planung wurde der Abdeckung des Planungszielvolumens (PTV) höchste Priorität zuerkannt: ≥ 95% des PTV mussten ≥ 95% der Dosis erhalten. Elektive Lymphabstromgebiete erhielten 54 Gy (1,8 Gy/Fraktion). Die Zielvolumendosis im Primärtumor und in pathologischen Lymphknoten betrug 70,5 Gy (2,35 Gy/Fraktion) = simultaner integrierter Boost. Nach Möglichkeit wurde die mittlere Dosis der Parotiden auf 26 Gy beschränkt. Die Funktion der Speicheldrüsen wurde durch Technetium-Szintigraphie ermittelt.
Ergebnisse: Es fand sich eine signifikante Dosis-Wirkungs-Beziehung zwischen der mittleren Dosis in der Parotis und der Wiederherstellung ihrer Funktion. Bei einer mittleren Dosis < 31 Gy kann mit einer 75%igen Wiederherstellung innerhalb von 12 Monaten gerechnet werden. Die Autoren beobachteten eine signifikante Korrelation zwischen Speichelfluss (SF) und prozentualem Anteil der Parotis, der eine Dosis < 26 Gy erhielt (V_{26}%). Um 75% des SF zu erhalten, sollten 46% des Parotisvolumens eine Dosis < 26 Gy erhalten.
Schlussfolgerung: Die Möglichkeit, mittels helikaler Tomotherapie die Funktion der Speicheldrüsen zu erhalten, hängt nicht nur von der applizierten mittleren Dosis, sondern auch vom prozentualen Anteil des Volumens ab, das < 26 Gy erhält.

Schlüsselwörter: Kopf-Hals-Tumoren · Helikale Tomotherapie · Parotisaussparung

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Introduction

Conventional head-and-neck (H&N) radiotherapy (RT) is associated with high doses to the major salivary glands resulting in xerostomia as major distressing complication, changes of taste, dental decay, oral infections, dysphagia, nutritional deficiencies, and impaired social activity [3, 4]. Parotid glands are responsible for ± 65% of the total amount of saliva. Reduction in salivary flow following radiation depends on dose, gland volume irradiated, and the glands' location relative to the target volumes [6, 7, 16]. Eisbruch et al. reported a mean dose of 28.4 Gy for a normal-tissue complication probability (NTCP) of 50% [6].

The use of sophisticated planning and delivery methods aims at delivering high doses to the clinical target and reducing dosage to healthy tissues. Several studies reported on conformal and/or intensity-modulated radiotherapy (IMRT) techniques to spare the parotid glands [13, 15, 21, 29, 34, 35].

The study aim is to investigate the potential of helical tomotherapy (Hi-Art Tomotherapy®, Madison, WI, USA) in preserving the parotid function while delivering the prescribed dose to the target.

Patients and Methods

Patient and Tumor Characteristics

Since 06/2005, 20 consecutive patients with a squamous cell carcinoma of the H&N region have been treated with helical tomotherapy. According to the H&N protocol, four patients received concomitant chemotherapy (cisplatin 100 mg/m^2, three cycles).

Seven patients without disease and a minimal follow-up of 12 months were included, 13 patients were excluded for the following reasons: death from intercurrent disease (n = 2), lung metastasis (n = 2), second primary (n = 1), in-field recurrence (n = 3), lost to follow-up (n = 3), and primary parotid carcinoma (n = 2).

Table 1. Patient and tumor characteristics.

Tabelle 1. Patienten- und Tumorcharakteristika.

Male/female (n)	6/1
Median age (range, years)	56 (46–74)
Tumor sites (n)	
• Oral cavity	2
• Oropharynx	2
• Larynx	1
• Hypopharynx	1
• Unknown primary	1
Stage (n)	
• II	1
• III	1
• IVA	4
• X	1
Radiotherapy (n)	
• Unilateral	4
• Bilateral	3

Patient and tumor characteristics are listed in Table 1. No medication – such as pilocarpine or amifostine that could affect salivary gland function – was administered [5, 26].

Treatment Technique

Target Delineation

A five-point thermoplastic cast (Orfit industries®, Wijnegem, Belgium) was used to immobilize patients. Treatment planning was based on contrast-enhanced computed tomography (CT) images with slice spacing and thickness of 3 mm. Delineation of the primary tumor, pathologic and elective lymph nodes was performed using co-registration of the CT scan with magnetic resonance images (MRI) and fluorodeoxyglucose positron emission tomography (FDG-PET) [10, 14]. The gross target volume (GTV 70.5), i.e., primary tumor and pathologic lymph nodes, was delineated and expanded to the clinical target volume (CTV 70.5) with 5 mm taking anatomic margins such as skin or bone into account. Delineation of the elective lymph node areas (CTV 54) was done according to recently published guidelines [11]. The planning target volumes (PTVs) were created from the CTVs by a volumetric expansion of 3 mm. Patients with an N0 neck were treated unilaterally. In case the primary tumor crossed the midline or in case of pathologic lymph nodes (one or more), the neck was irradiated bilaterally. As organs at risk (OARs) the spinal cord, parotids, thyroid gland, and esophagus were outlined on the planning CT.

Dose Prescription

A dose of 70.5 Gy in 2.35 Gy/fraction was prescribed to the primary tumor and the pathologic lymph nodes (PTV 70.5). The elective node regions were treated with 1.8 Gy/fraction up to 54 Gy (PTV 54): a simultaneous integrated boost scheme used in [9]. For the dose homogeneity within the PTV, the ICRU (International Commission on Radiation Units and Measurements) guidelines were followed [12]. Note that with tomotherapy the ICRU reference point cannot be defined and thus dose reporting is volume-based.

The normalized isoeffective dose, as for 2 Gy/fraction ($NID_{2\,Gy}$), was calculated according to Lee et al. with given formula:

$$NID_{2\,Gy} = D \cdot \frac{(d + \alpha/\beta)}{(d_{ref} + \alpha/\beta)} - \frac{(\ln 2) \cdot (T - T_{ref})}{\beta \cdot T_{pot}\,(d_{ref} + \alpha/\beta)}$$

{with d = dose per fraction; d_{ref} = reference dose per fraction (here = 2 Gy); α/β = 10 (for acute responding tissue); ln2 = 0.693; T = overall treatment time [calculated as $7 \cdot (n–1)/5$ with n = number of fractions]; T_{ref} = overall treatment time of the reference scheme; β = arbitrarily taken as 0.035 Gy^{-2}; T_{pot} = potential doubling time, taken as 4 days for the calculation}, gives us an $NID_{2\,Gy}$ of 75.4 Gy for the primary tumor and the pathologic lymph nodes and an $NID_{2\,Gy}$ of 50.9 Gy at the elective nodes [18].

Treatment Technique

The TomoTherapy Hi-Art System® is a treatment modality in RT in which IMRT is delivered in a helical fashion using a rotating 6-MV linac and a simultaneously moving couch. Beam modulation is obtained using a 64-leaf binary multileaf collimator (MLC) [23]. The combination of MLC, field width and table speed gives a high degree of dose modulation and shaping [8]. Positioning is integrated into the system by a CT detector mounted opposite to the beam, allowing the treatment beam to acquire a megavoltage CT scan (MV-CT) prior to treatment. By co-registration of these MV images to the kV-planning (kV-CT) images, positioning based on volumetric imaging is performed resulting in the high-precision positioning [31].

Dose calculation is performed by the tomotherapy treatment-planning system. This is an inverse planning system based on dynamically penalized likelihood optimization and performs dose calculation based on a collapsed-cone convolution algorithm [1, 22, 24]. Patients were planned using a field width of 2.5 cm and the calculation grid set to "normal". Pitch values ranged from 0.25 to 0.35 and the modulation factor ranged between 1.8 and 2.2, taking issues of homogeneity, conformity, and calculation time into account.

During planning the highest priority was given to a satisfying PTV coverage: deliver ≥ 95% of the prescribed dose to ≥ 95% of the target. Figure 1 shows dose distributions and a dose-volume histogram (DVH) in a bilaterally irradiated patient. The parotid glands were spared as much as possible while keeping an acceptable PTV coverage. If possible, the mean dose to the parotid gland was kept < 26 Gy [6, 7].

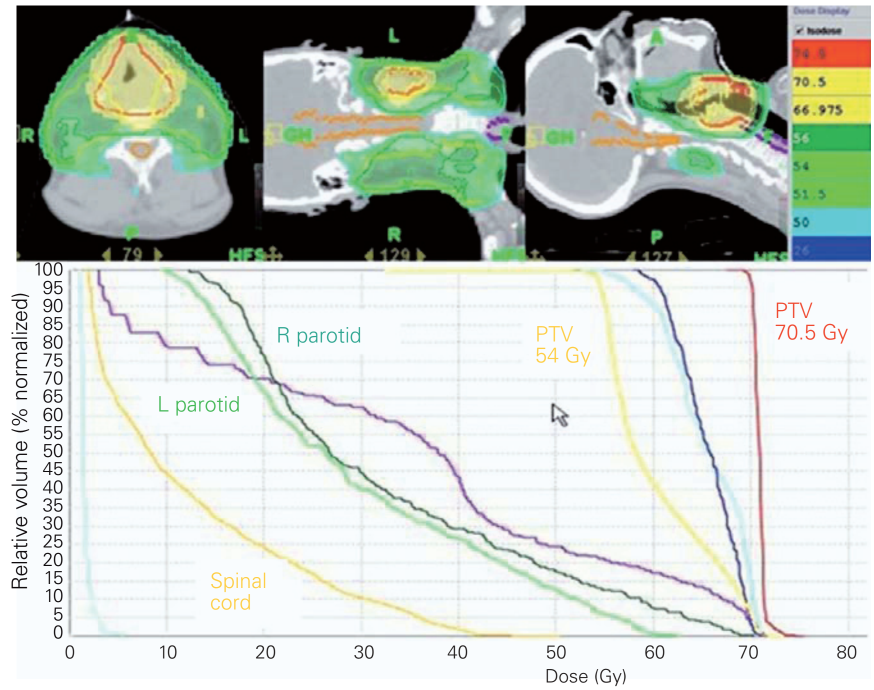


Figure 1. Dose distribution and dose-volume histogram of a tomotherapy plan.

Abbildung 1. Dosisverteilung und Dosis-Volumen-Histogramm eines Tomotherapie-Bestrahlungsplans.

Objective Scoring of Salivary Gland Function

Salivary gland scintigraphy was used to assess the function of both parotids [28, 32]. A series of planar views were acquired (60 s per view) during 45 min, starting immediately after intravenous administration of 185 MBq of ^{99m}Tc-pertechnetate. Tracer clearance from the glands following lemon juice administration (at 30 min) was calculated from regions of interest placed over each parotid. The clearance was calculated as the difference between the measured activity before and after lemon stimulation normalized to the measured activity before stimulation. This value was considered to represent a semi-quantitative measure of salivary gland function. Clearance values collected after RT were expressed as a percentage relative to baseline data.

Salivary gland scintigraphy was performed before RT (baseline) and every 4 months after RT. The baseline salivary excretion (SE) was taken as reference (100%). The values at the end of RT, at 4 months, 8 months, and 12 months are percentages of the initial baseline SE.

The correlation between mean RT dose and the percentage of volume receiving a certain dose is studied for both parotid glands.

Subjective Scoring of Salivary Gland Function

Patients filled in the EORTC quality of life questionnaire before, at the end of treatment, and every 4 months during follow-up [2]. The data were analyzed, but seven patients is too small a group to draw conclusions. The results did not contribute to this paper and were left out.

Statistical Analysis

To study differences, Student's paired one-tailed t-test was used. The level of significance was set at $p \leq 0.05$. To calculate the correlation between variables, the Pearson coefficient was used.

Results

Parotid Glands (n = 14): Dose and Volume Statistics

In patients 1–4, irradiated unilaterally, the contralateral parotids (n = 4) still received an average dose of 14.4 Gy (range: 8.2–17.2 Gy).

Table 2. Irradiation doses and volume statistics. Patients 1–4 were irradiated unilaterally, patients 5–7 bilaterally.

Tabelle 2. Bestrahlungsdosen und Volumenstatistiken. Patienten 1–4 wurden unilateral, Patienten 5–7 bilateral bestrahlt.

	Parotid gland neighboring the high-dose region		Contralateral parotid gland	
	Mean dose (Gy)	V_{26}%	Mean dose (Gy)	V_{26}%
Patient 1	39.9	50.4	17.2	100
Patient 2	50.9	0.0	8.2	100
Patient 3	38.7	37.8	16.7	100
Patient 4	32.9	47.4	15.1	100
Patient 5	39.2	34.8		
Patient 5'	38.6	29.3		
Patient 6	44.6	17.7		
Patient 6'	38.8	24.9		
Patient 7	29.8	69.9		
Patient 7'	29.2	68.0		
Average	38.7	38.0	14.4	

For the other ten parotids neighboring the high-dose region, the average mean dose given to the total parotid volume was 38.7 Gy (range: 29.2–50.9 Gy). The percentage of the total parotid volume receiving < 26 Gy ($V_{26}/V_{tot} \cdot 100 = V_{26}\%$) was, on average, 38.0% (range: 0–69.9%). No specific effort was made to keep the dose < 26 Gy (as previously mentioned: highest priority was to cover the PTVs with ≥ 95% of the prescribed dose). Table 2 summarizes the mean doses and the percentage of parotid gland volume that received a dose < 26 Gy.

Salivary Gland Scintigraphy

Dose-Response Relationship and Volume Effects in SE

There was a significant dose-response relationship between the mean dose given to the parotids and the functional recuperation (p = 0.005; Figure 2). For doses kept < 31 Gy, a recuperation at 12 months of at least 75% is measured.

There was also a significant correlation between the functional recuperation and the percentage of parotid gland receiving a dose < 26 Gy (V_{26}%; Figure 3). To maintain an SE > 75%, at least 46% of the parotid volume should receive < 26 Gy (p = 0.003).

Recuperation of SE

Figure 4 illustrates the recuperation of salivary gland function assessed by scintigraphy. In unilaterally treated patients, we observed an 18% decrease in SE in the contralateral parotids early after RT with an almost complete recovery (95%) 12 months later. Irrespective of the dose, the parotids neighboring the high-dose region showed a significant recuperation of SE at 12 months (p = 0.015).

Discussion

Seven patients treated with helical tomotherapy that reached 1 year of follow-up were evaluated. Significant improvement of the SE over time was noted. The mean dose given as well as parotid volume receiving > 26 Gy play a role in the capacity to recuperate after RT.

Several investigators showed that parotids have the capacity to recover from damage during the first years after RT. Most authors reported on the association between salivary flow and RT on salivary glands using three-dimensional

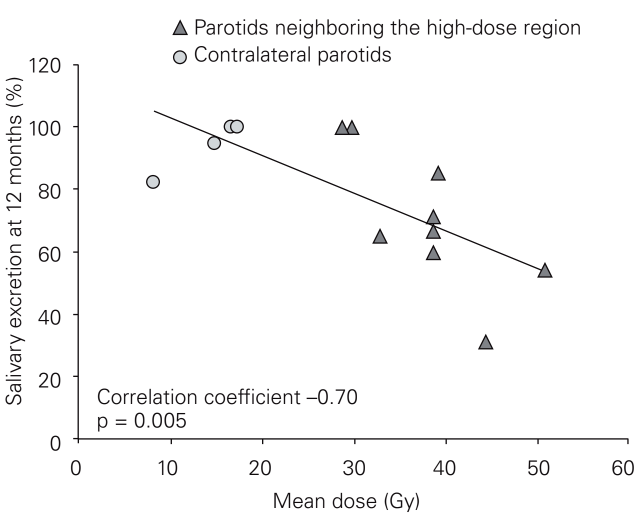


Figure 2. Correlation between mean dose and salivary excretion at 12 months.

Abbildung 2. Korrelation zwischen mittlerer Dosis und Speichelfluss nach 12 Monaten.

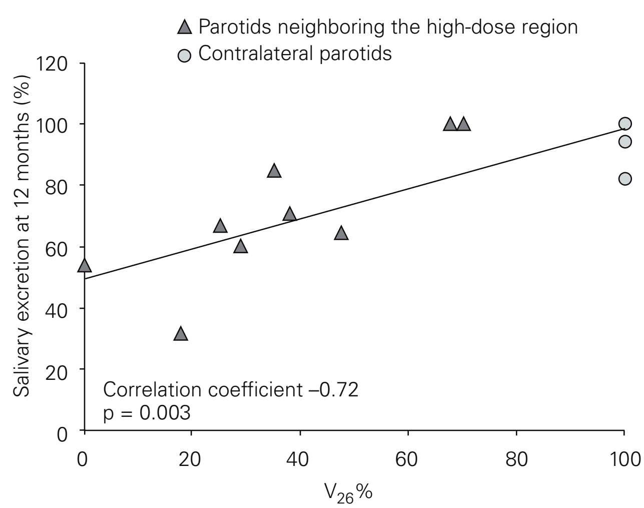


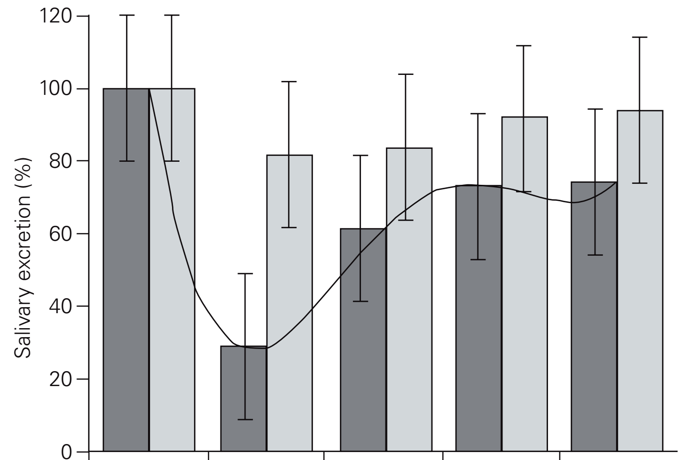
Figure 3. Correlation between irradiated volume of the parotid and salivary excretion at 12 months.

Abbildung 3. Korrelation zwischen bestrahltem Parotisvolumen und Speichelfluss nach 12 Monaten.

information derived from DVHs [6, 19, 27]. From these DVHs the NTCP is calculated and the NTCP of 50% is reported (i.e., the tolerance dose for 50% complication rate for the whole organ irradiated uniformly) [17]. In our study, no NTCP model is used because of the small patient number included.

Eisbruch et al. observed a mean dose of 26 Gy for a 75% reduction of salivary flow at 12 months [6]. Roesink et al. mentioned a mean dose of 43 Gy for a decrease of parotid function to 45% measured by scintigraphy [28]. Maes et al. reported on mean doses ≤ 20 Gy to have a preservation of the parotids of ≥ 70% [25].

We considered a reduction of SE < 25% after treatment acceptable, representing the ability of tomotherapy to spare glandular tissue. However, salivary scintigraphy is not widely used and no definition is available to classify post-treatment salivary function. Salivary recuperation (%) measured by scintigraphy, that is regarded as relevant, varies considerably by different authors and for data comparison, a consensus is warranted.



	Pre-RT	Post-RT	4 months	8 months	12 months
■ Parotids neighboring the high-dose region	100	28.9	61.1	72.7	74.1
□ Contralateral parotids	100	81.7	84.0	91.8	94.2

Time (months)

Figure 4. Recuperation of salivary excretion (%) after irradiation. At 12 months: p = 0.015. The baseline salivary excretion (Pre-RT) is taken as reference (100%). The values at the end of RT, and at 4, 8, and 12 months are percentages of the initial baseline salivary excretion.

Abbildung 4. Wiederherstellung des Speichelflusses (%) nach Strahlentherapie. Nach 12 Monaten: p = 0,015. Der Speichelfluss vor Behandlungsbeginn (Pre-RT) dient als Referenzwert (100%). Die Werte am Ende der Strahlentherapie, nach 4, 8 und 12 Monaten sind prozentuale Anteile des ursprünglichen Speichelflusses vor Behandlungsbeginn.

In the present study, 12 months after RT, a functional recuperation (74.1%) of the parotid gland becomes significant (our patients received an average mean dose of 38.7 Gy).

In all cases, the parotid glands still receive a substantial dose due to their anatomic position. They are located adjacent to the lymph node region level II, which is, in most cases, a "high-dose region" (54–70.5 Gy).

Functional recuperation observed in our study was high and might be explained by the very accurate patient positioning. Patient positioning is based on co-registration of acquired MV images to kV-planning image, resulting in very small mean deviations in patient daily positioning (data not published).

In addition, the intrafraction motion in H&N patients, immobilized with a five-point thermoplastic cast, was shown to be very accurate [20].

This accurate positioning based on MV-CT scan, and limited intrafraction motion allows to extend the CTV with only 3 mm to create the PTV. Helical tomotherapy further provides improved dose homogeneity and steep dose gradients. All this makes it possible to reduce margins surrounding the GTV and results in a decrease of mean parotid dose, as well as a smaller volume of the parotid receiving high doses [8, 30, 33].

Conclusion

By using helical tomotherapy, it is possible to preserve parotid function. Not only the delivered mean dose but also the volume percentage that receives a dose < 26 Gy is important. Further follow-up on a larger patient population is indicated to confirm this data.

Since the percentage of SE – measured by scintigraphy and considered relevant by different authors – varies considerably, a consensus is warranted for future comparison of data.

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