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ORIGINAL ARTICLE

Target coverage and local recurrences after radiotherapy for sinonasal cancer in Denmark 2008–2015. A DAHANCA study

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ABSTRACT

Purpose: The study aimed to investigate the pattern of failure and describe compromises in the definition and coverage of the target for patients treated with curatively intended radiotherapy (RT) for sinonasal cancer (SNC).

Methods and Material: Patients treated with curatively intended RT in 2008–2015 in Denmark for SNC were eligible for the retrospective cohort study. Information regarding diagnosis and treatment was retrieved from the national database of the Danish Head and Neck Cancer Group (DAHANCA). Imaging from the diagnosis of recurrences was collected, and the point of origin (PO) of the recurrent tumour was estimated. All treatment plans were collected and reviewed with the focus on target coverage, manual modifications of target volumes, and dose to organs at risk (OARs) above defined constraints.

Results: A total of 184 patients were included in the analysis, and 76 (41%) relapsed. The majority of recurrences involved T-site (76%). Recurrence imaging of 39 patients was evaluated, and PO was established. Twenty-nine POs (74%) were located within the CTV, and the minimum dose to the PO was median 64.1 Gy (3.1–70.7). The criteria for target coverage (V95%) was not met in 89/184 (48%) of the CTV and 131/184 (71%) of the PTV. A total of 24% of CTVs had been manually modified to spare OARs of high-dose irradiation. No difference in target volume modifications was observed between patients who suffered recurrence and patients with lasting remission.

Conclusion: The majority of relapses after radical treatment of SNC were located in the T-site (the primary tumour site). Multiple compromises with regards to target coverage and tolerance levels for OARs in the sinonasal region, as defined from RT guidelines, were taken. No common practice in this respect could be derived from the study.

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Introduction

Sinonasal cancer (SNC) is a collective term of rare tumours originating in the epithelium of the nasal cavity and the paranasal sinuses. Sinonasal tumours are histologically heterogeneous [1], and the biology of the disease varies accordingly. The five-year overall survival of Danish SNC patients has been investigated in previous studies, presenting five-year overall survival (OS) after curative treatment of 55% in 1995–2004 [2], and 56% in 2008–2015 [3]. Due to the rarity of the disease, the literature mostly comprises small retrospective series, and the level of evidence is generally low. The majority of patients are treated with a combination of surgery and postoperative radiotherapy (RT), except for small, localised tumours treated with surgery alone, and advanced unresectable tumours, treated with RT or chemo-radiotherapy alone. Primary neoadjuvant RT followed by surgery is rarely used.

The delivery of sufficient radiation dose to the target is often difficult, as critical organs at risk (OARs) including the brainstem, the chiasm, optic nerves and the eyes are located adjacent to the tumours. High-dose irradiation of these OARs might inflict permanent and potentially severe late toxicity [4,5], and sparing of these organs to some degree might be necessary to accommodate the patient's wishes of maintaining organ function. This is often only possible by deliberate compromises in the dose coverage. Thus, some compromises of the target coverage are expected and required. State-of-the-art RT today is intensity-modulated radiotherapy (IMRT), including volumetric-modulated arc therapy (VMAT), providing the opportunity for 3D sculpting of the dose, covering complex targets while reducing irradiation of critical OARs

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[6,7]. The target is defined as a clinical target volume (CTV), surrounded by a planning target volume (PTV). The PTV originates from an expansion from the CTV, to ensure sufficient dosage to the target regardless of intra- and interfractional anatomical changes, changes in patient positioning and uncertainties in dose delivery and contouring. Dose prescription and reporting is described by the ICRU for uncompromised target coverage [8]. This deliberate underdosage in SNC RT may be handled by splitting up the PTV into subPTVs, each prescribed with a dose corresponding to the overlapping, and higher prioritised, OAR [9]. No studies have described the presence of compromises in the treatment plans, and it has not been evaluated whether compromises have been achieved by intended reduced target coverage or modification of the target volumes. Therefore, the question remains how the compromises of target coverage and normal tissue sparing translate into risk and localisation of recurrences or severe toxicity.

This study aimed to establish pattern of failure with SNC patients treated with IMRT and describe different approaches to RT treatment planning, concerning the challenge of delivering sufficient radiation dose to the target while sparing OARs. Because of the different approaches to treatment planning, we were not able to perform any meaningful quality assurance; the perspective of the present paper was to illustrate the challenges and methodology in the treatment planning of RT for SNC to improve future treatment planning, reporting and quality assurance.

Material and methods

Patients

The study was performed as a retrospective cohort study. All patient data regarding the primary disease, treatment, recurrence and demographic data were retrieved from the DAHANCA database. The database encompasses all patients treated for head and neck cancer in Denmark, with a prospective collection of baseline data, information of diagnosis, and data on all treatment modalities [10]. Patients eligible for the current study were treated with curatively intended RT in 2008-2015 [3]. Inclusion criteria were tumours of the nasal cavity or maxillary, sphenoid, ethmoid, or frontal sinuses treated with primary or postoperative RT. Exclusion criteria were malignant melanoma, sarcoma, lymphoma, and treatment with palliative intent, or tumour of the nasal vestibule. The cohort was analysed overall and in subgroups of patients receiving postoperative RT and primary RT, as well as patients suffering relapse and patients with lasting remission. The study was approved by relevant regulatory authorities and reported according to the STROBE guidelines for observational studies [11] (Supplementary S1).

Radiotherapy

The vast majority of the cohort was treated with IMRT. Curatively intended RT was most often performed in combination with surgery. The indications for postoperative RT were evident or suspected positive resection margins (R1 or R2), as well as tumours classified as pT3 and pT4 [12]. Elective treatment of cervical lymph node regions was indicated with N2 and N3 disease, and in tumours infiltrating the oral cavity, the pharynx, or the skin, in addition to surgical neck dissection or high dose irradiation of GTV-N. Systemic treatment in the curative setting was not commonly used; however, concomitant chemotherapy could be prescribed, especially with neuroendocrine histologies.

All initial RT planning and delivery was performed following the national guidelines of DAHANCA [12–14]. The guidelines evolved during the period; recommendations for nomenclature and fractionation varied, and SNC was included as a specific indication in 2013. The issues regarding compromises evaluated in the current study were not described directly in any guidelines. The prescribed dose for primary RT was 66–68 Gy in 33–34 fractions, 5–6 fractions per week. For postoperative RT, patients with radical (R0) resections were treated with a prescribed dose of 60 Gy in 30 fractions, five fractions per week. In case of suspected microscopic or macroscopic residual tumour, the prescribed dose was 66 Gy in 33 fractions, five fractions per week. After termination of curative RT, imaging was performed 2–3 months after treatment, and further imaging only upon suspicion of recurrent disease. A total of 4/184 patients were treated with fractionation schedules not described above. All treatment plans were CT based. The target volumes in primary RT comprised gross tumour volume (GTV), CTV and PTV, and in postoperative treatment only CTV and PTV. According to the 2004 guidelines [14], the GTV-CTV margin was between 0–10 mm, and in the 2013 guidelines [13], the GTV to the high-risk CTV margin was 5 mm, modified for air and natural anatomical barriers. The CTV-intermediate risk was defined as the gross tumour with additional regions of potential microscopic spread and in postoperative radiotherapy the entire ipsilateral sinus. In the current study, the following OARs were evaluated: Brainstem, chiasm, optic nerves, and the posterior and anterior eyes.

Structures, including target volumes, originally delineated in the treatment planning systems for the original treatment plans were evaluated without editing. If delineation of the brainstem, chiasm, optic nerves or anterior or posterior eyes was not available, they were manually contoured according to Brouwer *et al.* [15]. All reported doses were original doses from the respective treatment planning systems, no re-calculation was performed.

Recurrence analysis

The DAHANCA database provided information on recurrences within the cohort. Recurrence imaging for the diagnosis of all T-site recurrences was collected, and as a part of the current study, T-site recurrences were delineated aided by the radiological descriptions. Recurrence imaging was rigidly registered with the planning CT using bony alignment measures, enabling dosimetric and geometric analysis of the delineated recurrence volume. Rigid registration was considered appropriate, as the T-site was located in areas

Table 1. Patient characteristics.

Patient characteristic (%)	All $n = 184$ (100)
Gender	
Male	118 (64)
Female	66 (36)
Primary T-site	
Nasal cavity	105 (57)
Maxillary sinus	59 (32)
Ethmoid sinus	13 (7)
Sphenoid sinus	5 (3)
Frontal sinus	2 (1)
UICC 1997 Stage at diagnosis	
I	19 (10)
II	29 (16)
III	23 (13)
IV	111 (60)
Unknown	2 (1)
T-stage at diagnosis	
1	21 (12)
2	29 (16)
3	25 (13)
4	32 (17)
4a	41 (22)
4 b	34 (19)
Unknown	2 (1)
Histology	
SCC	113 (61.5)
Adenocarcinoma	27 (15)
Adenocystic carcinoma	8 (4)
Undifferentiated carcinoma	8 (4)
Other	27 (15)
Unknown	1 (0.5)
Treatment	
Radiotherapy alone	39 (21)
Radiotherapy and surgery	91 (49)
Radiotherapy and chemotherapy	27 (15)
Radiotherapy, surgery and chemotherapy	27 (15)
Prescribed dose	
$\leq$60 Gy	41 (22)
63-66 Gy	84 (46)
$\geq$68 Gy	58 (31.5)
Unknown	1 (0.5)
Center	
1	51 (28)
2	36 (20)
3	45 (24)
4	44 (24)
5	8 (4)

surrounded by bony structures resulting in limited motion and multiple fixed alignment measure points. Rigid registration and delineation were performed using MIM Software (v 6.8.2). Patients with persistent disease were included in the imaging analysis as it aimed to investigate any treatment failure, demonstrating the complexity of SNC RT. Persistent disease was defined as treatment failure within three months from the last fraction of RT. The evaluation of recurrences and their relation to target volumes was performed on the total cohort as well as separately on patients treated with either postoperative or primary RT.

To analyse the origin of recurrence, the point of origin (PO) was estimated, defined as the point from which the recurrence originated and expanded. A mathematical method for the determination of the PO was used: Each delineated recurrence volume was pixelwise eroded, until one single point remained. This method was chosen because the traditional 'centre of mass' method would be misplaced due to the irregular tumour growth in the different cavities of the sinonasal area. It was recorded if the PO was placed inside or outside of the CTV and PTV, and the distances to the nearest edge of the CTV and to OARs (the brain stem, chiasm and the optic nerves and eyes) were registered. To evaluate the dose to the PO, the minimum dose delivered in the PO was recorded by expanding the point to a 6 mm sphere and reading the minimum dose from the dose–volume histogram [16].

Plan review

All treatment plans included in the study were retrospectively evaluated in a qualitative manner. Adjustments of target volumes were registered, that is, if the CTV or PTV were manually modified to spare OARs, namely the brain stem, the chiasm, the optic nerves, or the eye bulbs. The evaluations were performed by a clinical oncologist (MBS) by the following criteria: Target volumes that were deemed 'manually modified' were altered specifically to avoid critical OARs, and the alteration could not be explained by natural barriers or tumour growth. In addition, postoperative plans with 60 Gy volumes that did not include the entire ipsilateral sinus or nasal cavity were recorded. Since reasons behind modifications could not be discerned, modifications were only registered as present or not. An evaluation of dose coverage was performed by recording the volume receiving 95% of the prescribed dose (V95%); underdosage was present if 99% of the CTV received less than 95% of the prescription dose, or if 98% of the PTV (excluding the outermost 3 mm of the patient) received less than 95% of the prescription dose according to the 2013 guidelines.

All maximum doses were recorded as near max doses, that is, the dose delivered to 0.027 cm^3. For OARs, dose constraints from the DAHANCA guidelines was used. The dose constraints did not differ for the evaluated OARs between the 2004, 2013, and 2020 versions.

Statistical considerations

Patient demographics were analysed using descriptive statistics. The Chi Square test was used to analyse any differences in recurrence patterns between patients who received primary and postoperative RT and patients with recurrent disease and lasting remission. A p-value of 0.05 was considered statistically significant. All statistical analyses were performed using STATA (v 15).

Results

Altogether, 209 patients fulfilled the inclusion criteria, of whom 25 patients were excluded, as they did not complete full course RT for SNC or the treatment plans were unavailable (Supplementary S2).

Patient characteristics of the remaining 184 patients are shown in Table 1. The majority of patients were treated with primary surgery and subsequent RT (110/184, 60%), whereas 74/184 (40%) were treated with primary RT.

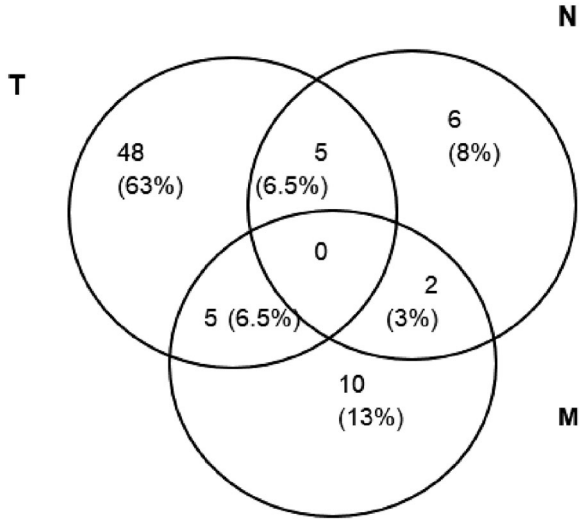

Figure 1. The pattern of failure in a cohort of 184 patients receiving curatively intended radiotherapy for sinonasal cancer, with 76 treatment failures. The numbers in circles represent the number of recurrence in that site, and the percentage denotes the distribution among the number of recurrences.

Pattern of failure

Treatment failure occurred in 76/184 patients (41%). A total of 19 patients (10%) had persistent disease, 56 (30%) recurrent disease and one patient (0.5%) with missing data. Figure 1 illustrates the pattern of failure within the cohort, showing that the majority of recurrences involved the T-site (58/76, 76%). The proportion of N-site involvement was 13/76 (17%), and distant metastases (M-site) occurred in 17/76 of the cases (22%). None of the patients had recurrent disease in both T, N, and M site simultaneously. The distribution of recurrences in T, N, and M site was similar in patients receiving either postoperative or primary RT; 37/74 patients receiving primary RT and 39/110 of patients receiving postoperative RT were diagnosed with recurrent disease.

Elective irradiation of the cervical lymph nodes was administered to 59/184 patients (32%), 23 of whom had nodal disease at the time of diagnosis. Altogether, 13 patients developed N-site recurrence, of whom seven patients (54%) had elective RT of the cervical lymph nodes. Of the 76 recurrences, salvage treatment was curatively intended in 29 patients (38%), palliative in 22 patients (29%), and 23 patients (30%) did not receive any treatment. Two (3%) were non-evaluable.

T-site recurrence analysis

Recurrence imaging of 39 patients with T-site recurrence was analysed. Patients who suffered recurrences solely in the N and/or M site were not included in this analysis. Imaging modalities varied between centres, comprising CT, MRI, PET-CT, and PET-MRI. The recurrence PO was localised within the CTV in 29/39 (74%) patients (Figure 2), and outside the CTV in 10/39 patients (26%). For recurrences located outside the CTV, the median distance from the PO to the edge of the CTV was 1.7 cm (range 0.3-5.2). The distance did not exceed 2.5 cm, except for two POs, located 5.2 cm and 2.9 cm from the edge of the CTV, respectively. A total of 28/39 POs (72%) were located within the 95% isodose curve, and for those located outside the 95% isodose curve, the median distance from the PO to the 95% isodose curve was 1.3 cm (range 0.3–3.3).

The minimum dose to the PO was median 64.1 Gy (range 3.1–70.7). A total of 19/39 patients received postoperative RT and 20/39 patients received primary RT. In patients who received postoperative RT, 13/19 patients had POs located within the CTV, the median distance for POs outside the CTV was 1.8 cm (range 1.1–2.9), and the minimum dose to the PO was median 59.2 Gy (range 3.1–68.7). For patients treated with primary RT, 14/20 patients had POs located within the CTV, the median distance for POs outside the CTV was 1.4 cm (range 0.3–5.2), and the minimum dose to the PO was median 66.5 Gy (range 27.8–70.7).

The location of recurrent tumours was analysed in relation to OARs (Supplementary S3). A total of 25/39 recurrences (64%) were located within 10 mm of the brainstem, chiasm, optic nerves, or the eye bulb, and 10 of those had manually modified target volumes, five altered CTVs and five PTVs. Within the group of POs located further away from OARs, seven manual modifications had been made to the volumes (altered CTVs, $n = 4$, PTVs, $n = 3$). POs close to the optic pathway received a minimum dose of 65.5 Gy median (range 3.1–70.7), and POs further from the optic pathway received a minimum dose of 59.7 Gy median (range 25.3–68.7).

Compromises in treatment planning

In 89/184 patients (48%), the CTV was not covered following the above-mentioned criteria, and for the unedited PTV, underdosage was present in 149 patients (81%) (Table 2).

Manual adjustments were recorded in 36/184 (20%) of the CTVs, and adjustments in PTV were frequent as well (Table 2). A total of 12 patients had adjustments in both the CTV and the PTV. The fraction of patients who suffered recurrence did not differ significantly between patients with and without compromises in the treatment plans (Table 2). Doses exceeding dose constraint levels in the brain stem, chiasm, optic nerve, or the eyes were present in 127/184 (69%) patients, the anterior and posterior eye being overdosed most often (Table 3).

The evaluation of doses above constraints and target volume adjustments across centres, suggested that different strategies were used (Supplementary S5). It should be noted that GTV-CTV margin practices varied considerably across centres during the period covered in the study [17].

Discussion

The evaluation of recurrences and the pattern of failure in patients treated with IMRT in the current study showed that treatment of sinonasal tumours remains a challenge. Providing sufficient dose to the target while sparing the OARs was in many cases obtained by adjusting and/or underdosing target volumes; yet, doses exceeding dose constraints to OARs were frequent. The majority of recurrences occurred in the T-site and the majority of T-site recurrence

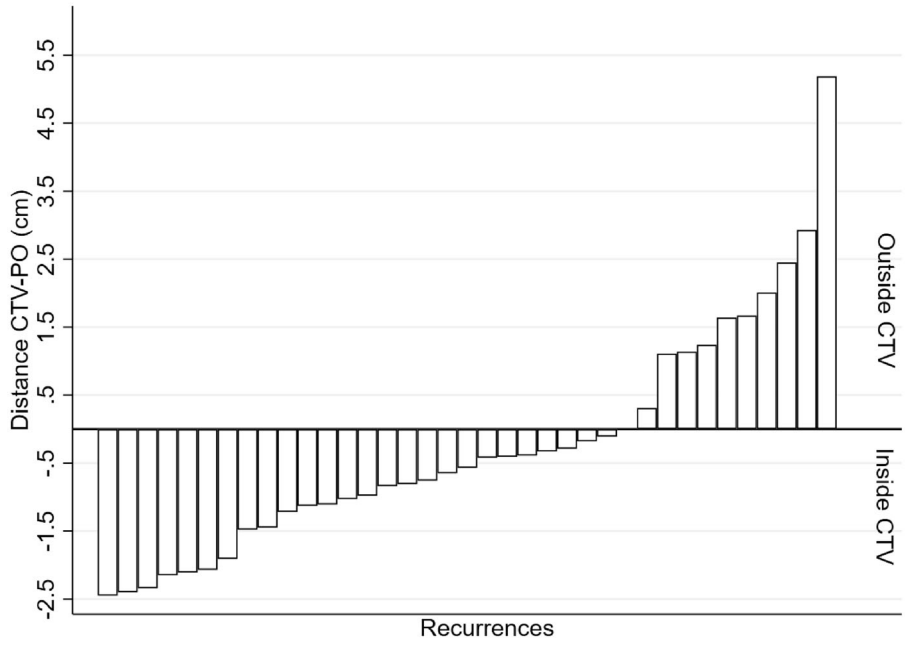

Figure 2. Distances to the edge of the CTV. Each bar represents a single PO. The reference line at Y = 0 represents the edge of the CTV, with negative values indicating a PO located inside the CTV and positive values indicating POs located outside the CTV. PO: point of origin, CTV: Clinical target volume.

Table 2. Compromises in treatment planning.

Parameter	All patients *n* (%)	Postoperative RT *n* (%)	Primary RT *n* (%)	*P*-value (Chi 2)	Treatment failure *n* (%)	Lasting remission *n* (%)	*P*-value (Chi 2)
Total	*n* = 184 (100)	*n* = 110 (100)	*n* = 74 (100)		*n* = 76 (100)	*n* = 108 (100)	
PTV V95% <98 %	149 (81)	85 (77)	64 (86)	0.4	61 (80)	75 (69)	0.9
CTV V95% <99 %	89 (48)	52 (47)	37 (50)	1.0	35 (46)	54 (50)	0.6
PTV modification	64 (35)	38 (35)	26 (35)	1.0	27 (36)	37 (34)	0.9
CTV modification	35 (19)	24 (22)	11 (15)	<0.01	15 (20)	20 (19)	0.3

Table showing the number of patients with CTV and PTVs with CTV V95% less than 99% and PTV V95% less than 98%, and the number of plans with modified target volumes. PTV: Planning target volume, CTV: Clinical target volume, V95%: Volume receiving 95% of the prescribed dose.

Table 3. Doses to organs at risk.

Organ at risk	Dose constraint [11]	No. of patients with dose above constraint (%)	D_{max} (Gy) for OARs with dose above constraint median (range)
Dose above constraint in any analysed OAR		127 (69)	
Brainstem	D_{max} 54 Gy	12 (7)	68.7 (55.0–72.97)
Chiasm	D_{max} 54 Gy	35 (19)	60.5 (54.8–70.9)
Optic nerve	D_{max} 54 Gy	91 (49.5)	
Ipsilateral			65.2 (54.5–73.8)
Contralateral			58.1 (55.0–69.1)
Eye back	D_{max} 45 Gy	103 (56)	
Ipsilateral			64.5 (45.7–75.6)
Contralateral			57.5 (46.6–69.1)
Eye front	D_{max} 30 Gy	108 (59)	
Ipsilateral			60.7 (31.7–73.0)
Contralateral			40.5. (30.6–69.3)

The total number of patients with doses above constraints in any analysed OAR and per OAR. Furthermore, the median D_{max} received by patients with doses above constraints in specific OAR is shown. D_{max}: D0,027 ccm, Gy: Grey, OAR: Organ at risk.

POs were located within the CTV. No difference in the location of POs were found in patients receiving primary or postoperative RT. The POs were primarily located in high-dose areas, suggesting that insufficient dose delivered to the tumour is one of the main factors in treatment failure, with relative radio-resistance potentially being a significant factor in treatment failures.

A number of different strategies concerning compromises in treatment planning were present, with no consensus regarding nomenclature and reporting of treatment planning strategy. The impact of these differences in terms of recurrence patterns could not be resolved in the present material, however, given the heterogeneity of the biology and strategies for treatment, this would require very large cohorts to make certain conclusions regarding a direct impact on local control. The aim of the current study was the description of strategies for treatment planning, in order to collect data to standardise the methodology and terminology and thus improve future SNC treatment planning and quality assurance. The risk of toxicity is present given the relatively high fraction of patients having high radiation doses to OARs. The toxicity was not evaluated in the current

study due to lack of relevant toxicity data in the DAHANCA database; a cross sectional study of toxicity in a similar cohort reported frequent late toxicity in SNC patients after curative RT [4,5]. The pattern of failure resembles other studies, as described below. Previous studies performed within the framework of DAHANCA investigated the outcome and pattern of failure of SNC in Denmark. Grau et al. [18] analysed the outcome of patients treated from 1982–1991, and Thorup et al. [2] evaluated patients treated in 1995–2004. The results from Thorup et al. are comparable to the current study, whereas Grau et al. reached a significantly lower OS, however, in a cohort including patients treated with palliative intent, and patients diagnosed with lymphomas and malignant melanomas as well. In the study by Thorup et al., T-site involvement was found in 81% of treatment failures. They found no significant difference in survival and locoregional failure between centres. Filtenborg et al. [3] reported outcome data in the current cohort, only also including patients treated with surgery alone, and found a five-year OS of 56% and T-site relapse in 81% [3].

In the present study, the majority of recurrences were located within the CTV, and the median minimum dose to the recurrences was 64.1 Gy. Most studies that investigated the pattern of failure in cancer sites of the lower neck characterised the large majority of relapses as in-field [19–22], one study investigating 16 relapses on the lower neck characterised most cases as marginal [22]. Thus, similar to our findings in SNC, relapses were located in high-dose areas. Fried et al. (2013) [23] investigated the pattern of failure in 79 patients diagnosed with SNC who received IMRT/3D conformal RT. A total of 8/15 had marginal or out-of-field recurrences, defined by the degree of overlap between recurrence-volume and the 95% isodose-curve. With our study, the majority of recurrences were located within the primary CTV as well as within the 95%-isodose curve, thus 'in-field'. Wiegner et al. (2012) [24] performed a study of 52 patients receiving IMRT for SNC. Their results were similar to the current study, as 25% had local recurrence, and 15% were located within the high-risk CTV, as compared to our results with 58/184 (32%) of the cohort having T-site recurrences only and 15% located within the CTV. Zukauskaite et al. investigated the location of recurrences after treatment for oral cavity, pharynx, and larynx cancer in relation to the GTV; they found that 51% of the POs were located within the GTV contour, and an analysis of the GTV-CTV margin displayed no difference in local recurrence rate with different margin extensions [17], indicating that margin size did not influence the pattern of failure. Different methods of estimating the PO were investigated by Zukauskaite et al. [16] and Due et al. [25] for lower head and neck tumours. Zukauskeite et al. found similar doses to the PO for each estimation method (65.8–66.2) and equal precision in estimating the PO [16]. Due et al. noted that evaluation based on the overlap of recurrence and target volumes tended to estimate the PO more peripheral because recurrences diagnosed later will tend to have larger overlapping areas due to a longer period of recurrence progression. With SNC, both the origin of a recurrence and the recurrence growth is restricted by bony structures, and recurrent tumours might appear irregular, complicating the estimation of the PO. The mathematical approach was chosen for the current study because of a high degree of reproducibility, despite the missing consideration of biological factors.

The extension and indication for elective irradiation of cervical lymph nodes are continuously discussed, as lymph node infiltration is not common at the time of diagnosis [26]. In the current study, 13/76 recurrences (17%) included lymph node metastases. The benefits of elective treatment of cervical lymph nodes have been discussed in several works; Cantu et al. [27] and Dooley et al. [28] did not recommend elective irradiation of cervical lymph nodes due to the low occurrence of N-site recurrences. On the contrary, Ahn et al. [26] performed a large retrospective analysis of 1382 patients and concluded that elective treatment of the neck should be considered, and Jegoux et al. [29] agreed, however, only for certain histologies. The number of lymph node metastases in a given institution could be affected by the imaging modality used in the process of diagnosing the primary disease, as more thorough imaging would theoretically be able to detect early disease in the lymph nodes and include them in the primary treatment. In the current study, 32% of the entire cohort received elective irradiation of cervical lymph nodes, 54% of those suffered N-site failure. To evaluate the correlation between N-site failures and elective radiotherapy, an analysis of the location of the affected lymph nodes, the extent of elective radiotherapy, and dosimetric analysis would be relevant.

The major strength of the current study lies in the prospective nationwide inclusion of data of all patients treated for SNC in Denmark, minimising selection bias. The high heterogeneity of the cohort regarding both histology, anatomical location and treatment with a combination of three different modalities (RT, surgery and chemotherapy) represents a limitation of the study. The guidelines changing in the study period and the lack of specific guidance in the compromise between target and critical OAR is a limitation of the study. However, the evaluation criteria for the analysed OARs were unchanged, and dose and fractionation schedules were very similar. The main issue regarding the guidelines is that the nomenclature and strategies for managing compromises in RT of SNC are not defined or described. In the current study, patients with both postoperative and primary treatment schedules were included, resulting in a considerably different risk or density of tumour cells in the target volumes. In principle, patients receiving primary radiotherapy have 100% risk of tumour cells in the GTV, whereas patients receiving postoperative radiotherapy may have very few or no tumour cells in the high-risk volumes. Patients treated with postoperative therapy would thus have a lower tendency of developing recurrence even with lower target dosage. To control for this, an analysis of patients with primary and postoperative treatment would be relevant. The results indicate that treatment planning of SNC has been based on individual compromises of target dosage versus sparing of the OARs. Future evaluation of target coverage and clinical compromises would be improved with stricter

guidelines concerning target definition, for example, a CTV-un-edited/per-protocol, CTV-optimisation and an unedited PTV (that may be underdosed), meeting the definitions according to ICRU 83(8). This would allow for quality control of the radiotherapy planning, comparison of planning strategies of photon or proton treatment, and better options for future guidelines.

In conclusion, radiotherapy of SNC is complex, and multiple compromises must be made. The majority of relapses were located in the T-site, and 74% were within the CTV. The clinical compromises were handled differently between centres, indicating a need for guidelines to define treatment planning and opitmisation strategy as well as rules for common nomenclature for future evaluation purposes.

Disclosure statement

The authors report no conflict of interest.

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