Nasal Cavity and Paranasal Sinuses

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Overview

Epidemiology

Tumors of the nasal cavity and paranasal sinuses are relatively uncommon, with an incidence of 0.75/100.000 in the USA [1]. They are usually diagnosed after the age of 40. The nasal cavity consists of four subsites; the nasal vestibule, the lateral walls, the floor, and the septum. Paranasal sinuses are named after their locations as maxillary, ethmoid, sphenoid, and frontal. Tumors originating from the maxillary sinus are the most common among all, having an incidence approximately twice as the nasal cavity tumors. Ethmoid sinus lesions are the second most common tumors, and tumors of other locations are extremely rare. The etiologic factors are comprised of occupational exposure such as wood dust, glues, nickel, chromium, mustard gas, isopropyl alcohol, and radium [2–6]. Thorotrast, an agent historically used in radiographic studies for maxillary sinus imaging, also was associated with maxillary sinus carcinomas. Tobacco and alcohol consumption are shown to increase the risk of nasal cancer.

Pathological and Biological Features

Majority of these tumors are squamous cell carcinomas (SCC). Basal cell carcinoma, adnexal carcinoma, minor salivary gland neoplasms (i.e., adenocarcinoma (the second most common), adenoid cystic carcinoma (the third most common), and mucoepidermoid carcinoma), melanoma, neuroendocrine carcinoma (i.e., small cell carcinoma, esthesioneuroblastoma, and

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sinonasal undifferentiated carcinoma), lymphoma, sarcoma, and plasmacytoma are less common histopathologic entities.

Definitive Therapy
Radiotherapy is the preferred treatment modality over surgery for tumors of nasal vestibule in order to obtain better cosmesis with equal local control rates. For large tumors with deep invasion, surgery, in combination with neoadjuvant or adjuvant radiotherapy, is the treatment of choice. For small tumors of ethmoid sinuses and other sites of nasal cavity, results of radiotherapy and surgery are equivalent. Small tumors of maxillary sinuses may be treated with surgery alone. Chemoradiotherapy is an option for patients who refuse surgery.

Adjuvant Therapy
Surgery and adjuvant radiotherapy is the standard treatment for locally advanced maxillary sinus tumors. Postoperative radiotherapy is also indicated for positive surgical margins, lymphatic invasion, or perineural invasion. Chemotherapy has a limited role for the tumors of this region.

1 Case Presentation

A 27-year old male admitted to the hospital with swelling and redness in the left eye. He was also suffering from headache in the frontal region periodically. There was no vision loss or diplopia. He had no significant medical history other than an adenoidectomy 20 years ago.

His physical and endoscopic examination revealed a mass in the left middle meatus. The nasal septum was slightly deviated to the right. Nasal passages were narrowed. The nasopharynx, oropharynx, oral cavity, and larynx were intact. There were no pathologic lymph nodes in his neck.

The MRI detected a giant mass completely obliterating the superior 2/3 portion of the left nasal cavity and eroding the superior nasal conchae (Fig. 4.1). It also invaded the medial wall of the left maxillary sinus and extended through the sinus. The left orbit was invaded via erosion of its medial wall, and medial extraocular muscles were displaced. Lamina papyracea, ethmoid cells, bony structure at the base of frontal lobe, crista galli, cribriform plate, left ethmoid foveae, left half of sphenoid, and frontal sinuses were also invaded with intracranial extension. Multiple conglomerated lymphadenopathies in the left cervical chain and submandibular region were present.

Biopsy from the nasal mucosa revealed undifferentiated carcinoma. Endoscopic resection was performed. The pathology revealed the same histology.

He was diagnosed with T4bN2bM0 maxillary sinus carcinoma.

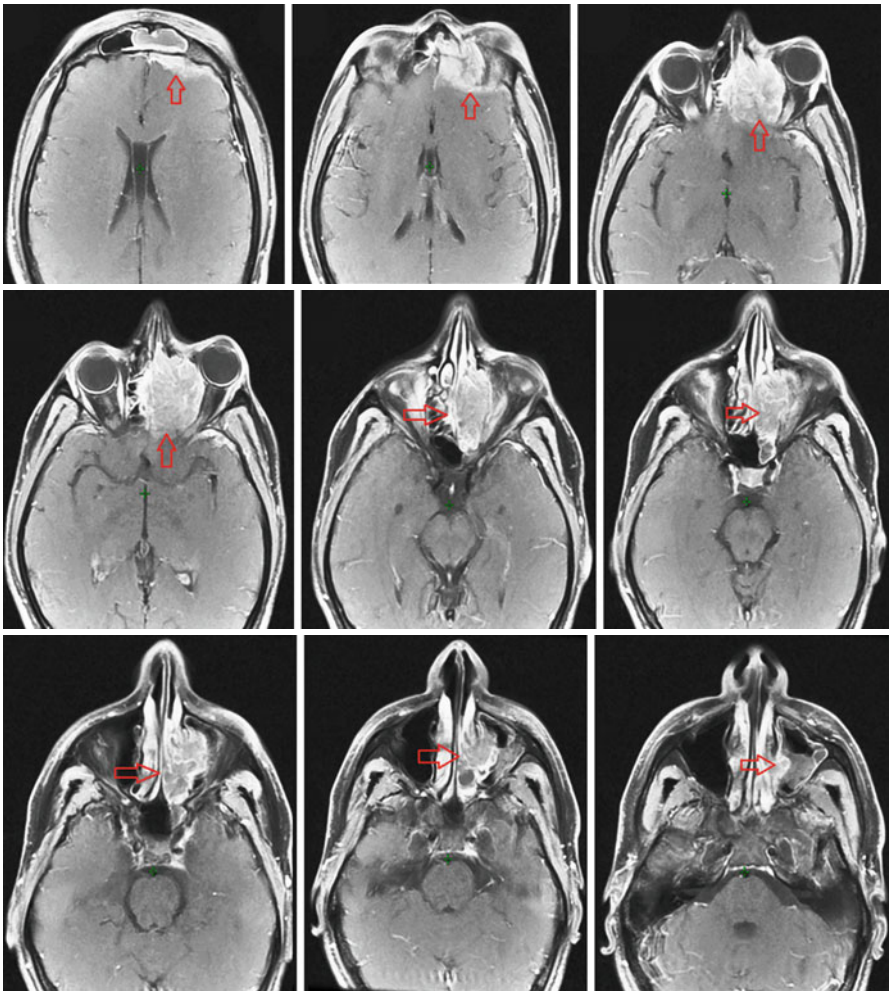

Fig. 4.1 A giant mass completely obliterating the superior 2/3 portion of the left nasal cavity and eroding superior nasal conchae seen on MRI

2 Evidence-Based Treatment Approaches

Nasal Vestibule Tumors

Primary radiotherapy (RT) is preferred for small superficial tumors because of cosmetic concerns. However, surgery may also lead to high local control (LC) rates with excellent cosmetic results in selected cases. The size and location of the tumor

guide us to choose the appropriate technique of RT. Brachytherapy (BRT) and external beam radiotherapy (EBRT) have similar cure rates reaching to 90 % for tumors up to 2 cm. For tumors larger than 2 cm, higher doses are needed to reach 80 % LC rates [7–11].

Large tumors with deep extensions require surgery in combination with neoadjuvant or adjuvant RT. Mazeron et al. evaluated 1,676 patients with nasal vestibule and skin of the nose cancers who were treated with BRT or EBRT. They reported 93 % overall LC rate. Tumors smaller than 2 cm and located externally (skin of the nose) have better LC rates (96 % for <2 cm vs. 81 % for >4 cm, and 94 % for skin of the nose vs. 75 % for the vestibule). However, LC rate with surgery only was no more than 90 % [12].

Nasal Cavity Tumors

Surgery and RT have similar results for small tumors in terms of cure. Daly et al. reported 91 % 5-year overall survival (OS) rates with either treatment modality [13]. Surgery may be preferred for posterior nasal septum tumors, whereas BRT is the treatment of choice for anterior and inferior septum tumors not larger than 1.5 cm. For lateral wall tumors, EBRT rather than BRT is preferred because of cosmetic concerns. In a study of 45 patients who were treated with solely RT, or RT combined with surgery, 5-year OS rate was 75 % [14]. In this study, Ang et al. reported that lateral wall and floor tumors had inferior prognosis compared to septum tumors (LC rates, 68 % vs. 86 %). For stages II–IVa, surgery should be performed with or without adjuvant RT.

Paranasal Sinus Tumors

Surgery and adjuvant RT are the treatment of choice for ethmoid sinus tumors. If cosmetic or functional result is an issue, RT alone or concurrent chemoradiotherapy (CRT) may be an option [15]. Choussy et al. reported tumor extension, lymph node involvement, and the presence of brain invasion as prognostic factors for ethmoid tumors. They found nearly half of the patients who received adjuvant RT after surgery had recurrences, 75 % of which were local [16]. Blanco et al. reported 5-year LC, DFS, and OS rates as 61, 35, and 29 %, respectively, in 106 patients with paranasal sinus cancers who received RT [17].

Surgery alone is efficient for early-stage maxillary sinus tumors. Adjuvant RT is indicated in patients with locally advanced disease. Combination therapy has better 5-year LC and OS rates than single treatment modalities, both ranging from 44 to 80 %. 5-year LC and OS rates with RT alone were reported as 39 and 40 %, respectively. Parsons et al. reported survival rates of 60, 70, 30, and 40 % for T1, T2, T3, and T4 lesions treated with surgery and RT, respectively [18]. In locally advanced tumors, solely RT results are dismal with 5-year survival rates of 10–15.

Intensity-modulated radiation therapy (IMRT) is accepted as the standard RT modality. A previous study from UCSF observed no difference in LC rates between IMRT and conventional RT [13]. 2- and 5-year LC rates were 62 and 58 %, respectively. However, the complication rate was significantly different with fewer complications in IMRT arm. In 2010, Dirix et al. reported 2-year LC and OS 76 and 89 %, respectively, with postoperative IMRT [19]. Madani et al. found 5-year LC and OS rates of 70.7 and 58.5 %, respectively, in 105 patients more than half of whom had ethmoid sinus tumors [20]. Also in 2012, Duprez et al. showed 5-year LC and OS as 59 and 52 %, respectively [21]. Claus et al. reported their IMRT experience in 62 patients with sinonasal cancers following R0 resection [22]. With PTV doses of 60–70 Gy, they found that none of the patients with cribriform plate invasion were locally controlled. However, 5-year actuarial LC rate was 84 % in patients without cribriform plate invasion.

Stereotactic body radiotherapy (SBRT) may also be an alternative option particularly to spare optic pathway structures. Ozyigit et al. published their experience on 27 patients with paranasal sinus or nasal cavity tumors whom they treated with CyberKnife® (Accuray, Sunnyvale, CA, USA) [23]. Six patients received RT for recurrence. Median dose was 31 Gy in median 5 fractions. They reported local relapse-free rates of 76 % for 21.4 months in median. Overall survival rates in 1 and 2 years were 95.2 and 77.1 %, respectively, with acceptable complication rates.

Chemotherapy

The role of chemotherapy (CT) in nasal cavity and paranasal cancers is limited. Neoadjuvant CT may be used for reducing the tumor size in order to assist surgery in terms of removal of the tumor with less morbidity and also to lend a hand to radiation oncologists in terms of decreasing normal tissue toxicity. In locally advanced tumors, the LC rates are better with concurrent CRT compared to neaodjuvant CT. For unresectable tumors, and medically inoperable patients, CRT is an option.

3 Target Volume Determination and Delineation Guidelines

Gross Tumor Volume (GTV)

GTV should include the gross tumor and involved lymph nodes detected by clinical and endoscopic examination, CT, MRI, PET/CT, and intraoperative findings, if operated. GTV is divided into two: GTVp defines the primary tumor, and GTVn defines the involved lymph nodes. In postoperative cases, GTV is not stated as it is assumed that the primary lesion or grossly involved lymph nodes are removed.

Following structures should be evaluated carefully whether they are involved in case of specific tumors:

- Maxillary Sinus:
  - Anteriorly:
    Is subcutaneous tissue involved?
    Is there extension to the skin of cheek (leading to destruction in zygomatic arch)?
  - Laterally:
    Is the pterygoid fossa involved?
    Is there tumor extension to the sphenoid sinuses?
  - Medially:
    Are the middle meatus and the nasal septum intact?
  - Posteriorly:
    Is the posterior wall intact?
    Are the pterygoid plates, pterygopalatine fossa and muscles involved?
    Is there extension into the infratemporal fossa (through the cribriform plate)?
    Are the clivus and C1 vertebra involved?
    Does the tumor extend to the nasopharynx?
  - Superiorly:
    Are the floor and medial wall of the orbit intact?
    Is the ethmoid sinus involved?
    Is the cribriform plate intact?
  - Inferiorly:
    Is the hard palate involved?
    Is there loosening of the first and second molar teeth (which points out invasion of maxilla)?
- Ethmoid Sinus:
  - Anteriorly:
    Is frontal sinus involved?
    Is there extension to the anterior orbit?
    Is the anterior cranial fossa intact?
    Does the tumor extend to the maxillary sinus?
    Is the palate involved?
  - Laterally:
    Are the orbital medial wall and floor involved?
    Does the tumor extend to the nasal cavity or the orbital rectus muscle?
  - Medially:
    Is contralateral ethmoid sinus intact?
  - Posteriorly:
    Is the sphenoid sinus involved?
    Are the pterygoid plates intact?
    Is there extension into the orbital apex, brain, middle cranial fossa, or clivus?
    Is the cranial nerve (CN) I (olfactory) involved?
    Is the dura involved?
    Does the tumor extend to the nasopharynx?
  - Superiorly:
    Is the cribriform plate intact?

– Inferiorly:
  Is the maxillary sinus involved?
  Is there extension to the nasal cavity?
  Does the tumor extend to the hard palate?

Clinical Target Volume (CTV)

Three CTVs are defined based on risk definitions. CTV1 covers the primary tumor bed with a 1–1.5 cm margin given circumferentially around the GTV.

- *CTV1* for the lymph nodes is the high-risk regions with a gross lymph node, or levels with positive lymph nodes and extracapsular extension (ECE) following lymph node dissection.
- *CTV2* covers the entire operative bed as it is the region of high risk for subclinical disease and potential routes of spread. If the ethmoid sinus or olfactory region is involved, the cribriform plate is also included. For paranasal sinus tumors, CTV2 includes all other sinuses, if explored during surgery. If orbital exenteration was performed because of orbital invasion, the bony orbit is also delineated. In case of craniofacial resection, the frontal graft should also be included. CTV2 for the lymph nodes should include ipsilateral submandibular and subdigastric lymph nodes for squamous cell and poorly or undifferentiated carcinomas. The lower neck should be contoured in case of invasion of the palate, nasopharynx, skin of the cheek or the anterior nose, or gingiva.
- *CTV3* is the low-risk regions for subclinical disease. In case of perineural invasion (PNI), a CTV3 is delineated in order to encompass the whole tract of the submandibular nerve to the skull base. In all adenoid cystic histologies, local nerve pathway to the skull base should be delineated, as these tumors are highly neurotrophic.

In patients who received neoadjuvant CT, CTV is defined depending on the pre-chemotherapy volumes.

Planning Target Volume (PTV)

A margin of 3–5 mm is added in all directions. However, it may be minimized to 1 mm or may even be omitted in areas adjacent to critical structures such as the optic nerves.

Case Contouring

Delineation of target volumes of T4bN2bM0 maxillary sinus carcinoma is shown in Figs. 4.2 and 4.3a–c.

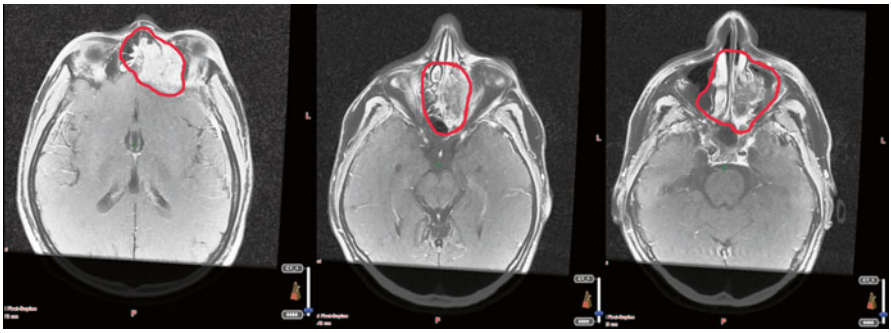

Fig. 4.2 Fused MR simulation CT images of GTV for T4bN2bM0 maxillary sinus cancer

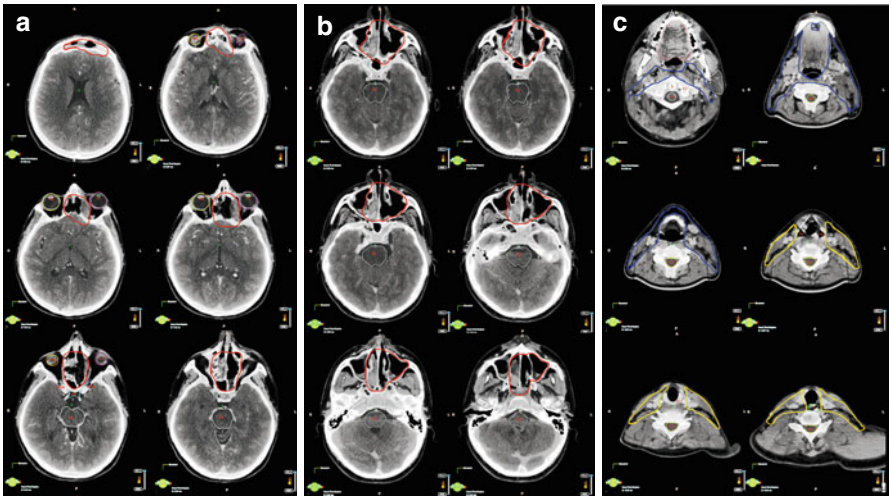

Fig. 4.3 (**a**–**c**) Delineation of target and normal volumes for T4bN2bM0 maxillary sinus cancer. (Surgical bed: $CTVp_{60Gy}$ *red line*; bilateral levels I, II, and RPLN: $CTVn_{60Gy}$ *blue line*; bilateral levels III, IV, and V: $CTVn_{54Gy}$ *orange*)

4 Treatment Planning

- *Guidelines for Target Volume Doses*: Guidelines for target volume doses are summarized in Table 4.1.
- *Guidelines for Normal Tissue Constraints*: Guidelines for normal tissue constraints are summarized in Table 4.2.
- *Treatment Planning Assessment* (Figs. 4.4 and 4.5)
  - *Step 1*: Check whether the targets are adequately covered: All plans should be normalized to at least 95 % of the volume of PTV70 which is covered by the

Table 4.1 Guidelines for target volume doses

TNM	CTV1 (70 Gy/33–35 fr)	CTV2 (59.4–63 Gy/33–35 fr)	CTV3 (54–56 Gy/33–35 fr)
T1–2 N0	GTVp	–	–
T3–4 N0	GTVp	1–1.5 cm	Ipsilateral I–II, RPLN
Tany N+	GTVp, GTVn	Ipsilateral adjacent lymph nodes (the one level above, and the one level below)	Remaining lymph nodes (ipsilateral, contralateral, and RPLN for advanced tumors)

RPLN retropharyngeal lymph nodes

Table 4.2 Guidelines for normal tissue constraints

Structure	Constraints
Brain	Mean <50 Gy For large volumes, <30 Gy
Brain stem	Maximum <54 Gy (no more than 1 % to exceed 60 Gy)
Spinal cord	Maximum <45 Gy (no more than 1 % to exceed 50 Gy)
Eyes	Maximum <50 Gy
Lenses	Maximum <10 Gy, try to achieve <5 Gy (as low as possible)
Optic nerves	<50 Gy Maximum <54 Gy
Optic chiasm	<50 Gy Maximum <54 Gy
Parotid glands	Mean of one gland <26 Gy 50 % volume of one gland <30 Gy 20 cc of both glands <20 Gy
Submandibular and sublingual glands	As low as possible
Each cochlea	Volume receiving 55 Gy <5 %
Mandibula and temporomandibular joint	Maximum <70 Gy (no more than 1 cc to exceed 75 Gy)
Oral cavity (excluding PTVs)	Mean <30–40 Gy No hot points receiving >60 Gy in oral cavity region
Lips	Mean <20 Gy Maximum <30 Gy
Esophagus, postcricoid pharynx	Mean <45 Gy
Glottic larynx	Mean <45 Gy
Brachial plexus	Maximum <66 Gy

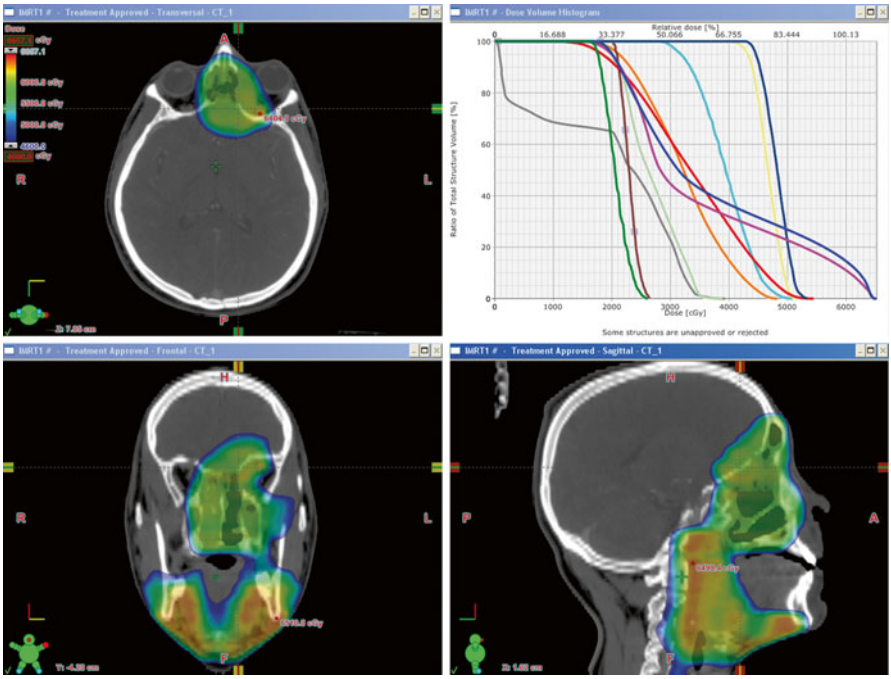

Fig. 4.4 Sagittal, coronal, and axial sections of IMRT plan for T4bN2bM0 maxillary sinus cancer

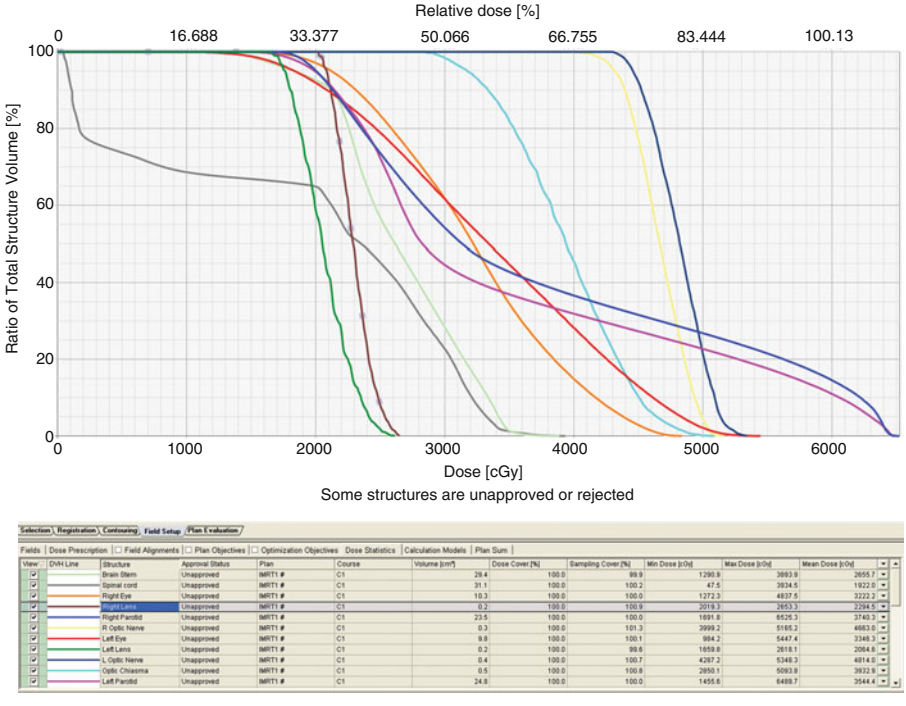

Fig. 4.5 Dose volume histogram for T4bN2bM0 maxillary sinus cancer

70 Gy isodose surface and 99 % of PTV70 needs to be at or above 65.1 Gy. It is confusing to evaluate all PTV DVHs, and one may end up slight underdosing of PTV2 and PTV3 when a uniform 3 mm margin is added, which is generally 80 % coverage of PTV2 and PTV3 mostly due to parotid or critical structure sparing. However, if your nodal CTVs are relatively generous including some muscle outside of the nodal fat plane, much of the setup error is "built in" to the CTV contour drawn, so some physicians only evaluate CTV2 and CTV3 by looking at dose distributions on the treatment plan and not PTV DVH. It is very important to evaluate the DVH of PTV1, because a very tight margin on CTV1 could result in underdosing of gross disease due to daily setup error. Be careful to ensure that PTV1 should receive at least >90 % of prescribed dose.

  - *Step 2*: Check whether there is a large hot spot: No more than 20 % of PTV70 is at or above 77 Gy, and no more than 5 % of PTV70 is at or above 80 Gy.
  - *Step 3*: Check whether the normal tissue constraints are met.
  - *Step 4*: Check whether the hot/cold spots exist in the wrong place (slide by slide looking at isodose distribution): The hot spots need to be arranged in the GTV, and it is necessary to make sure that the hot spot is not on a nerve in the CTV.
- *Case Plan*: The case presented here was treated with IMRT as shown in Fig. 4.6a–c. Surgical bed as $CTVp_{60Gy}$ was prescribed 60 Gy; bilateral levels I, II, and RPLN were irradiated as $CTVn_{60Gy}$ and received 60 Gy; bilateral levels III, IV, and V as $CTVn_{54Gy}$ received 54 Gy.
- *Treatment Algorithm*

Nasal Cavity and Ethmoid Sinus
T1–2, N0, M0
Surgery (in case of close or + surgical margin or PNI add adjuvant RT)
RT
T3–4, N0, M0
If resectable, surgery + adjuvant RT
If unresectable, RT with or without concurrent cisplatin 100 mg/m^2 on days 1, 22, and 43 (or cisplatin 40 mg/m^2/week or carboplatin 100 mg/m^2 on days 1, 8, 15, 22, 29, and 36 or cetuximab 250 mg/m^2/week after a loading dose of 400 mg/m^2 1 week before RT)
Any T, ≥N1, M0
Surgery + adjuvant RT with or without concurrent cisplatin 100 mg/m^2 on days 1, 22, and 43 (or cisplatin 40 mg/m^2/week or carboplatin 100 mg/m^2 on days 1, 8, 15, 22, 29, and 36 or cetuximab 250 mg/m^2/week after a loading dose of 400 mg/m^2 1 week before RT)
CRT (concurrent cisplatin 100 mg/m^2 on days 1, 22, and 43) (or cisplatin 40 mg/m^2/week or carboplatin 100 mg/m^2 on days 1, 8, 15, 22, 29, and 36 or cetuximab 250 mg/m^2/week after a loading dose of 400 mg/m^2 1 week before RT)
Maxillary Sinus
T1–2, N0, M0
Surgery (in case of close or + surgical margin, PNI, or adenoid cystic histology add adjuvant RT)
T3–4, N0, M0
If resectable, surgery + adjuvant RT with or without concurrent cisplatin 100 mg/m^2 on days 1, 22, and 43 (or cisplatin 40 mg/m^2/week or carboplatin 100 mg/m^2 on days 1, 8, 15, 22, 29, and 36 or cetuximab 250 mg/m^2/week after a loading dose of 400 mg/m^2 1 week before RT)

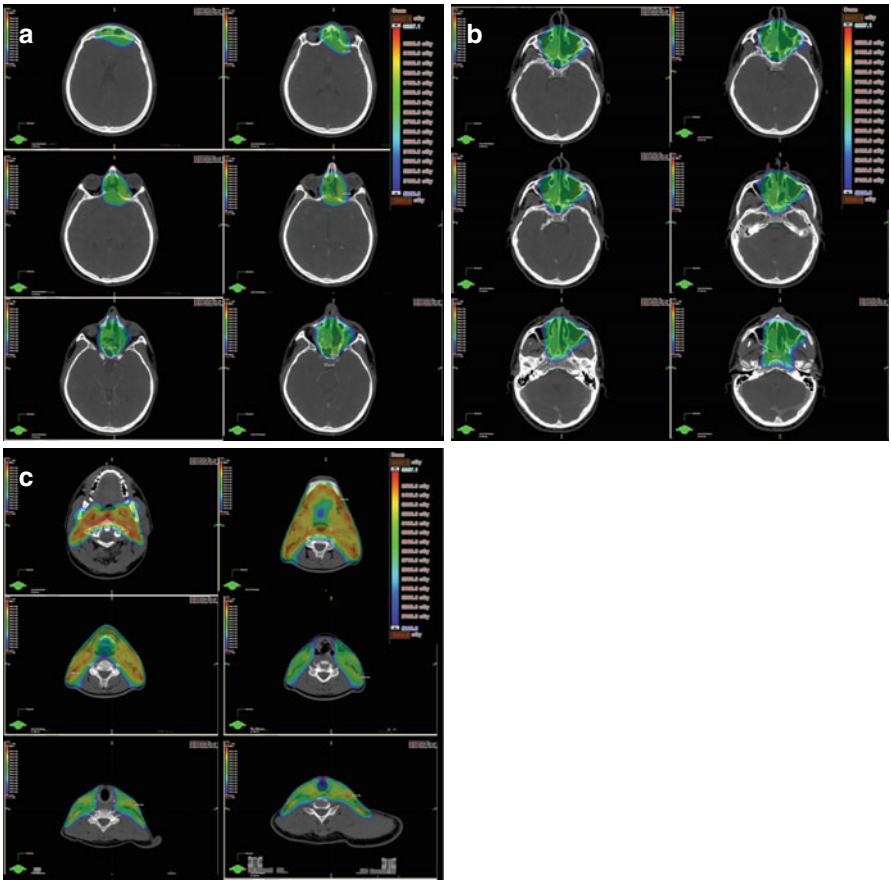

Fig. 4.6 (**a**–**c**) Serial slices of dose color wash from IMRT plan for T4bN2bM0 maxillary sinus cancer

If unresectable, RT/CRT (concurrent cisplatin 100 mg/m^2 on days 1, 22, and 43) (or cisplatin 40 mg/m^2/week or carboplatin 100 mg/m^2 on days 1, 8, 15, 22, 29, and 36 or cetuximab 250 mg/m^2/week after a loading dose of 400 mg/m^2 1 week before RT)
Any T, ≥N1, M0
Surgery (with neck dissection) + adjuvant RT with or without concurrent cisplatin 100 mg/m^2 on days 1, 22, and 43) (or cisplatin 40 mg/m^2/week or carboplatin 100 mg/m^2 on days 1, 8, 15, 22, 29, and 36 or cetuximab 250 mg/m^2/week after a loading dose of 400 mg/m^2 1 week before RT)
CRT (concurrent cisplatin 100 mg/m^2 on days 1, 22, and 43) (or cisplatin 40 mg/m^2/week or carboplatin 100 mg/m^2 on days 1, 8, 15, 22, 29, and 36 or cetuximab 250 mg/m^2/week after a loading dose of 400 mg/m^2 1 week before RT)

- *Follow-Up*: Every 3 months for the first 2 years, every 4 months for year 3, every 6 months for years 4–5, and then annually. Complete remission through

clinical and endoscopic examination and imaging studies is necessary. Distinguish viable residual or slowly regressing tumor, or post-therapy changes by MRI and PET/CT.

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