Metastatic Cancer in Neck Node with Occult Primary

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Overview

Epidemiology

Metastatic cervical carcinoma of unknown primary (MCCUP) represents 3 % of all tumors and 2–9 % of all head and neck cancers (HNC). Currently, no risk factor has been identified except those defined for subsites of HNC. Patients must be evaluated for Epstein-Barr virus (EBV), human papillomavirus (HPV), and sexual behaviors, which may provide useful clues about the primary. Typically, majority of cases are 55–65 years aged males with history of chronic tobacco and/or alcohol use presenting with uni- or bilateral painless mass(es) in the upper two third neck.

Pathological and Biological Features

Histologically, squamous cell carcinoma (SCC) accounts for 53–77 % of all MCCUP followed by undifferentiated carcinomas (20 %). Other pathologies are rare, but a diagnosis of adenocarcinoma in the lower third of the neck is important as it usually denotes for a primary below the clavicles. Histologic examination of the biopsy specimen for EBV and HPV is important for tailoring the further diagnostic search and treatment plans.

Definitive Therapy

Currently, there exists no standard treatment recommendation for MCCUP. Treatment is directed by two most significant prognostic factors, namely, nodal stage (N) and status of extracapsular extension (ECE). For N1 disease and ECE (−), single-modality treatment with selective neck dissection (ND) or involved field radiotherapy (RT) is indicated. For N1 but ECE (+) and N2-3 disease, a combined approach with pre- or postoperative RT/CRT or

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upfront CRT followed by planned ND for only those without clinical/metabolic complete response is justified. For unilateral tumors, bilateral neck RT decreases the contralateral recurrences with no proven survival advantage. Similarly, despite commonly practiced, clinical impact of inclusion of pharyngeal mucosal sites in the RT portal is debated.

Adjuvant Therapy
Benefit of adjuvant or consolidation chemotherapy is uncertain but warrants to be addressed in future trials as nearly 25–30 % of patients present with distant metastases at some time point during the follow-up period.

1 Case Presentation

A 44-year-old male who has 20 pack/year smoking history with no significant past medical history presented with a painful mass in his right upper neck, which had gradually enlarged for nearly 8 months. He had no problems with dysphagia, swallowing, chewing, phonation as well as any chest pain, palpitations, or dyspnea.

His physical examination and rhinoscopy revealed normal ear and nasal findings. He had no dental problem. There were no lesions of the gingiva, buccal mucosa, floor of mouth, oral tongue, base of tongue, hard palate, soft palate, tonsillar fossa, or posterior oropharyngeal wall by visualization or palpation. There was an approximately 2 cm hardly mobile painful node in the left upper level II–III area and was no other palpable adenopathy on his left neck. Examinations of cranial nerves II–XII are grossly normal. On endoscopic examination, there was no evidence of disease in the oropharynx, larynx, and hypopharynx, and vocal cords were mobile, but mucosal surfaces were irregular on the left posterior wall of nasopharynx, which was randomly biopsied for two times with no evidence of malignancy.

On MRI and PET-CT, multiple hypermetabolic lymph nodes on left levels IIA, IIB, and III, greatest of which was measured 30×21 mm, were defined, but primary tumor origin could not be determined (Fig. 11.1).

A biopsy was performed from these lymph nodes confirming the metastatic carcinoma of squamous cell type.

He was staged as N2bM0 MCCUP.

2 Evidence-Based Treatment Approaches

Treatment plans are mainly tailored by the involved lymph node site and its association with probable primaries (Table 11.1), stage of neck (Table 11.2), surgical margin and extranodal extension (ECE) status, and presence/absence of residual disease. Neck dissection (ND) is the preferentially recommended treatment option for N1 patients with SCC histology, RT being an alternative Category 2B. RT is also

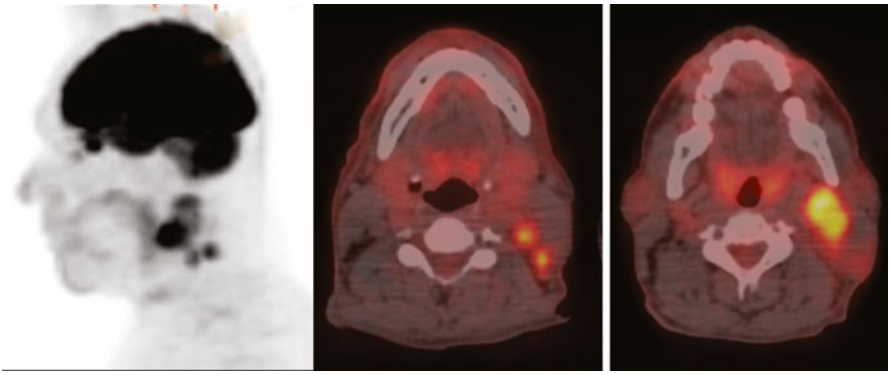

Fig. 11.1 Multiple hypermetabolic lymph nodes on left levels IIA, IIB, and III

Table 11.1 Nomenclature of neck lymph node regions and their relation with possible primary tumor sites

Level	Involved nodes	Possible primaries
1A	Submental	Lower lip, anterior tongue, floor of mouth
1B	Submandibular	Anterior alveolar mandibular ridge Oral cavity, anterior nasal cavity, submandibular glands
2A-B	Jugulodigastric/ upper jugular	Oral cavity, nasal cavity, nasopharynx, oropharynx, Hypopharynx, larynx, major salivary glands Oropharynx, nasopharynx
3	Middle jugular	Oropharynx, nasopharynx, oral cavity, Larynx, hypopharynx
4	Lower jugular	Larynx, hypopharynx, thyroid Cervical esophagus
5A-B	Posterior triangle	Nasopharynx, oropharynx, subglottic larynx, Apex of pyriform sinus, thyroid, cervical esophagus
6	Anterior compartment	Glottic and subglottic larynx, apex of pyriform sinus, thyroid, cervical esophagus
Retropharyngeal	Medial, lateral retropharyngeal	Nasopharynx, oropharynx, soft palate, hypopharynx

indicated in medically unfit patients or in technically unresectable N1 disease. In surgically treated patients, adjuvant treatment indications depend on the status of gross residue, surgical margins, ECE, and pathological nodal involvement. For N1 and ECE (−) patients, both observation and RT are options. For N2-3 and ECE (−) cases, RT or CRT (Category 2B) may be alternatives. If ECE (+), CRT is the treatment of choice (Category 1), but RT may be an option for cases unsuitable for chemotherapy. If gross residue left or surgical margins are positive, re-resection and/or CRT should be performed. In any patient planned to receive RT or CRT at upfront/adjuvant settings, it is mandatory to consider the tumor size, involved nodal

Table 11.2 Nodal staging for MCCUP (AJCC 7th edition)

Nodal disease	Nodal characteristics
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2a	Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension

Abbreviations: AJCC American Joint Committee on Cancer, *MCCUP* Metastatic cervical cancer of unknown primary, *N* nodal stage

station(s), and HPV and EBV status for the design of RT field. Salvage ND is indicated in clinical or metabolic evidence of residual disease following RT or CRT.

CRT is the preferred upfront treatment option for all medically fit patients with N2–3 disease (Category 2B). Induction chemotherapy (Category 3) followed by RT or CRT is alternative recommendation for such patients. Salvage ND should be considered in patients with incomplete response.

In N1 and early N2A disease, either ND or RT alone provides excellent regional control rates. For ECE (−) N1-2a disease, neck recurrence rates following either modality ranges from 0 to 15 % [1, 2]. In adequately dissected ECE (−) cases, postoperative RT is not necessary as does not increase local control rates or survival [1, 3]. In ECE (+) patients, postoperative concurrent CRT is mandatory to increase local control rates [1].

In patients with advanced neck disease (N2b-N3), combined modality treatment with postoperative CRT or definitive CRT followed by planned ND for residual, unresponsive, or progressive tumors is the standard treatment approach with the best neck control and survival outcomes. In a series of 224 patients treated with RT alone, Grau et al. reported 5-year neck control and overall survival rates of 50 and 37 %, respectively [4]. In two recent smaller series with 40 and 60 patients, Aslani et al. [5] and Lu et al. [6] reported encouraging 5-year local control (76.3 and 65.3 %) and overall survival (77.8 and 68.5 %) rates, which may be associated with significant improvements in diagnostics and RT techniques. As a reflection of site specific data from advanced HNC which suggest significantly better locoregional control and survival rates with CRT than RT alone, it is rational to anticipate similar outcomes for MCCUP patients [7–9]. In series of definitive concurrent CRT or postoperative CRT, the 2- to 5-year rates of 89–100 % neck control and 74–92 % overall survival are excellent [10].

A summary of results of RT and CRT series of MCCUP are summarized in Table 11.3.

Although extensive-field RT including the bilateral neck and potentially involved mucosal sites is the widely practiced RT option, the question whether the irradiation

Table 11.3 Outcomes of patients with MCCUP following RT or CRT

	Outcome
Neck control[a]	
N1-2a	90–100 %
N2b-c	80 %
N3	50–60 %
Distant metastasis	
N1-2a	<10 %
N2b-c	15 %
N3	25 %
5-y overall survival	40–60 %
Emergence of primary[b]	
Median time	21 months
2-y	<10 %
5-y	15 %
10-y	20 %

Abbreviations: CRT chemoradiotherapy, *MCCUP* metastatic cervical cancer of unknown primary, *N* nodal stage, *RT* radiotherapy, *y* year
[a]Decreases with unilateral irradiation
[b]Decreases with irradiation of mucosal sites

be uni- or bilateral neck and whether potential mucosal sites be irradiated has not answered yet. Data from two literature reviews favor bilateral neck irradiation and inclusion of mucosal sites over unilateral neck irradiation alone [10, 11], but care must be given as different studies may have suffer from biases of inclusion of patients with poor overall health status or heavy/inoperable necks in unilateral neck irradiation group.

RT technique of choice is another question. However, a recent study by Ligey et al. demonstrated that use of 3D-RT or IMRT were associated with significantly superior regional control ($p = 0.026$) and survival outcomes ($p = 0.029$) compared to 2D-RT [12]. Based on the available data on specific HNC sites, IMRT has the similar potential to offer lesser acute and late toxicity rates for MCCUP patients, especially for cases in whom bilateral neck and/or mucosal sites are planned to be irradiated [13, 14]. Therefore, we recommend the use of 3D-RT as minimum standard, preferably IMRT where available.

Primary tumor emergence at mucosal sites is generally in the range of 0–12 % [15], increasing by time and decreasing with involvement of mucosal sites in the RT portal (Table 11.3). In series of Wallace et al., mucosal control rates for neck only and selective mucosal irradiation were 92 and 100 %, respectively [16]. Because majority of unknown primaries emerge at tonsils and base of tongue, the authors included nasopharynx and oropharynx in their selective radiation portal and included larynx and hypopharynx only in cases with level 3 nodal involvements. On the other hand, as their incidence rates are similar, it is rather difficult to discriminate true mucosal emergence of MCCUP from second primaries of head and neck area [17].

3 Target Volume Determination and Delineation Guidelines

Gross Tumor Volume (GTV)

GTV should encompass the any grossly involved lymph node(s), namely, >1 cm on shortest diameter with a necrotic center or metabolically active on PET scans, and with any apparent soft tissue extensions. All data from clinical and endoscopic examination, CT, MRI, and/or PET-CT should be comprehensively used for accurate GTV definition. Co-registered images may provide higher chance for correct delineation of GTV.

Clinical Target Volume (CTV)

Based on the risk definitions, 3 CTV volumes need to be defined:

- *CTV1:* For definitive RT/CRT or postsurgical patients with positive margins, CTV1 corresponds to GTV plus a margin of ≥5 mm at all directions, which may be reduced to as low as 1 mm in close proximity to critical structures. In postsurgical setting with soft tissue invasion or ECE (+), CTV1 is the surgical bed with a margin of ≥5 mm at all directions and represents for high-risk CTV1. In the absence of adverse factors, CTV1 is the surgical bed with a margin of ≥5 mm around and represents for intermediate risk CTV1.
- *CTV2:* It represents the high-risk region for subclinical disease including microscopic disease and potential routes of spread for likely primary and nodal disease. Potential primary regions should include the entire nasopharynx, base of tongue, ipsilateral tonsillar fossae, pyriform sinus, and highly suspected regions depending on the location and laterality of involved lymph node(s). For definitive RT/CRT or postsurgical patients with positive margins, CTV2 corresponds to soft tissues and nodal regions adjacent to CTV1. For soft tissue component, 0.5- to 1-cm margin around and for nodal component 2–3 cm from CTV1 nodal basins should be included in CTV2. In postoperative setting, CTV2 includes elective nodal regions and potential primary regions for both high- and intermediate-risk IMRT, as defined above.
- *CTV3:* Lower-risk elective nodal regions such as bilateral low anterior neck or contralateral neck in cases with unilateral lymph node involvement form the CTV3.

Planning Target Volume (PTV)

PTV is formed by additional margin around the CTVs to compensate for the intra- and/or inter-fraction variability, uncertainties of treatment setup, and internal organ motion. It is better for institutions to define their own PTV margin, which may

Table 11.4 Suggested lymph node levels to be included in radiotherapy portal according to suspected primary site

Suspected primary	N1-2a	N2b-3
Nasopharynx	1, 2, 3, 4, and RPN	2 3, 4, 5, and RPN
Oral cavity	1, 2, and 3 (4 if anterior tongue suspected)	1, 2, 3, 4, and 5
Oropharynx	2, 3, and 4 (RPN if posterior PWT suspected)	1, 2, 3, 4, 5, and RPN
Hypopharynx	2, 3, and 4	1, 2, 3, 4, 5, and RPN
Larynx	2, 3, and 4	2, 3, 4, and 5

Abbreviations: PWT posterior pharyngeal wall tumor, *RPN* retropharyngeal nodes

highly differ between RT centers. In general, a minimum of 5 mm at all directions is used to define each PTV. However, as it is critical to consider organs at risk, PTV margins can be reduced as needed. Respective PTV1, PTV2, and PTV3 are created by adding abovementioned margins to CTV1, CTV2, and CTV3.

Any MCCUP or primary HNC almost never involve all lymph node regions (level 1a to 6).

It should be kept in mind that the risk of ECE increases with size. Almost >50 % of lymph nodes between 1 and 3 cm are ECE (+), which increases to >75 % in tumors >3 cm [18–22].

Probable primary tumor sites according to involved lymph node station(s) are summarized in Table 11.1.

In addition to primary involved nodal basins, the probable intermediate risk or elective nodes to be involved in typical IMRT portal according to suspected primary sites should be defined as described in Table 11.4.

If bilateral node stations are involved, tumors of midline structures such as nasopharynx, hypopharynx, hard or soft palate, floor of mouth, and supraglottic larynx should specifically be remembered.

If exclusive level IV involvement is present, probable tumor site should highly be suspected below the clavicles.

Representative target volumes for MCCUP case presented here are shown in Fig. 11.2.

Level Definition Tips

Level IB (submandibular) is separated from level IIA by the submandibular gland and jugular vein interface, level II (subdigastric-jugulodigastric) follows the jugular vein to the jugular fossae, hyoid bone and upper border of cricoid cartilage separates level II from III (midjugular), level IV (low jugular and supraclavicular) lays between lower border of cricoids cartilage and clavicle, and level V (posterior cervical) nodes are located behind posterior edge of sternocleidomastoid muscle.

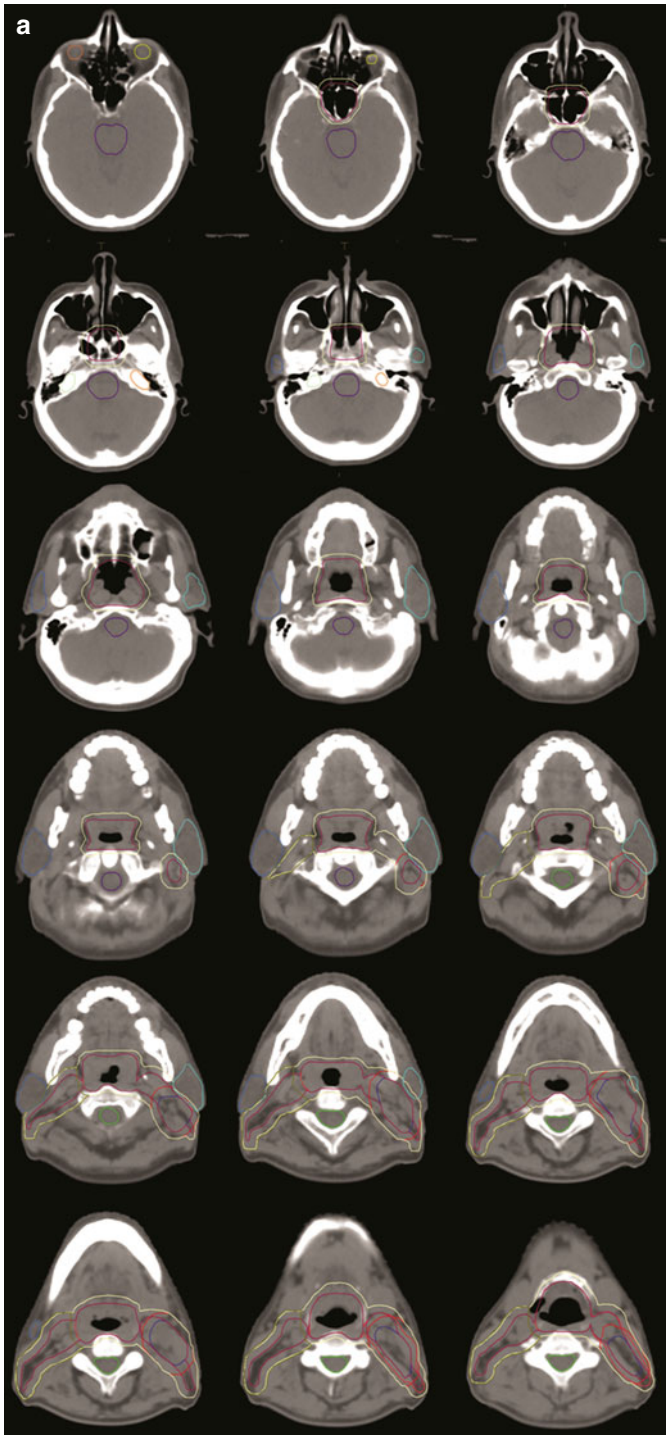

Fig. 11.2 Representative target volumes for metastatic cervical cancer of unknown primary case presented here (**a**, **b**)

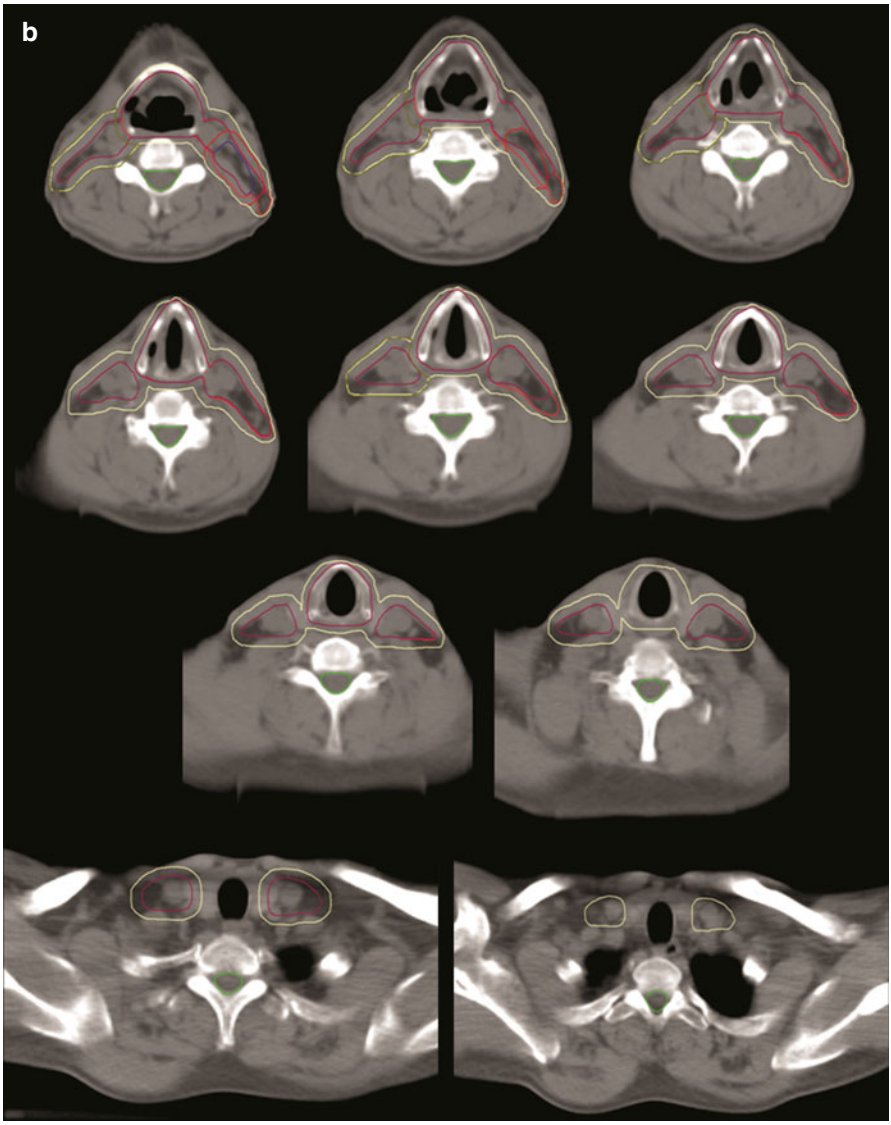

Fig. 11.2 (continued)

Case Contouring (Fig. 11.2)

- Check coverage of nasopharynx
- Check coverage of base of tongue
- Check coverage of uni- or bilateral tonsils

- Check coverage of pyriform sinus
- Check coverage of additional head and neck structures based on nodal involvement
- Check coverage of the midline structures in case of bilateral nodal involvement

4 Treatment Planning

- *Guidelines for Radiotherapy Doses:* To minimize dose to the critical structures, particularly the parotid glands, IMRT (preferred) or 3D-RT is recommended. This is critical especially when oropharyngeal structures are included in radiation portal. Dose distribution of PTV_{70}, $PTV_{59.4}$, and PTV_{54} Gy and related dose-volume histogram for the case presented here are demonstrated in Figs. 11.3 and 11.4, respectively. Typical recommended doses of RT for definitive RT/CRT and postoperative settings are described in Table 11.5.

Definitive Radiotherapy

- *High-Risk PTV*: Includes involved lymph nodes and possible local subclinical infiltration at the high-risk level lymph node(s). A total of 66 Gy (2.2 Gy/fr) or 70 Gy (2 Gy/fr or 2.12 Gy/fr if dose-painting IMRT or simultaneous integrated boost IMRT used. If the planned dose is >70 Gy, in an effort to minimize the risk of toxicity, some authors recommend use of slightly decreased daily doses (e.g. <2 Gy) at least during some part of treatment.
- *Mucosal Sites*: Depending on the field size, putative mucosal sites should receive 50–66 Gy (2 Gy/fr) with standard 3D-RT or sequentially planned IMRT. For highly suspicious mucosal sites, 60–66 Gy should be considered. If dose-painting IMRT or simultaneous integrated boost IMRT is utilized, doses of 54–66 Gy (1.63–2 Gy/fr in 33 fractions) are recommended as indicated.
- *Low-Intermediate Risk PTV*: All suspected sites of subclinical spread including the nasopharynx, base of tongue, tonsils, pyriform sinus, and bilateral neck nodes (levels I–V):
  - In cases of 3D-RT or sequentially planned IMRT: 44–50 Gy in 2 Gy daily fractions
  - If IMRT is dose painting or simultaneous integrated boost: 54–63 Gy in 1.6–1.8 Gy daily fractions

Definitive Concurrent Chemoradiotherapy

- *High-Risk PTV:* Typical dose is 70 Gy (2 Gy/fr) for 3D-RT or dose painting IMRT/simultaneous integrated boost (2.12 Gy/fr). Doses beyond 70 Gy is not recommended with concurrent CRT.

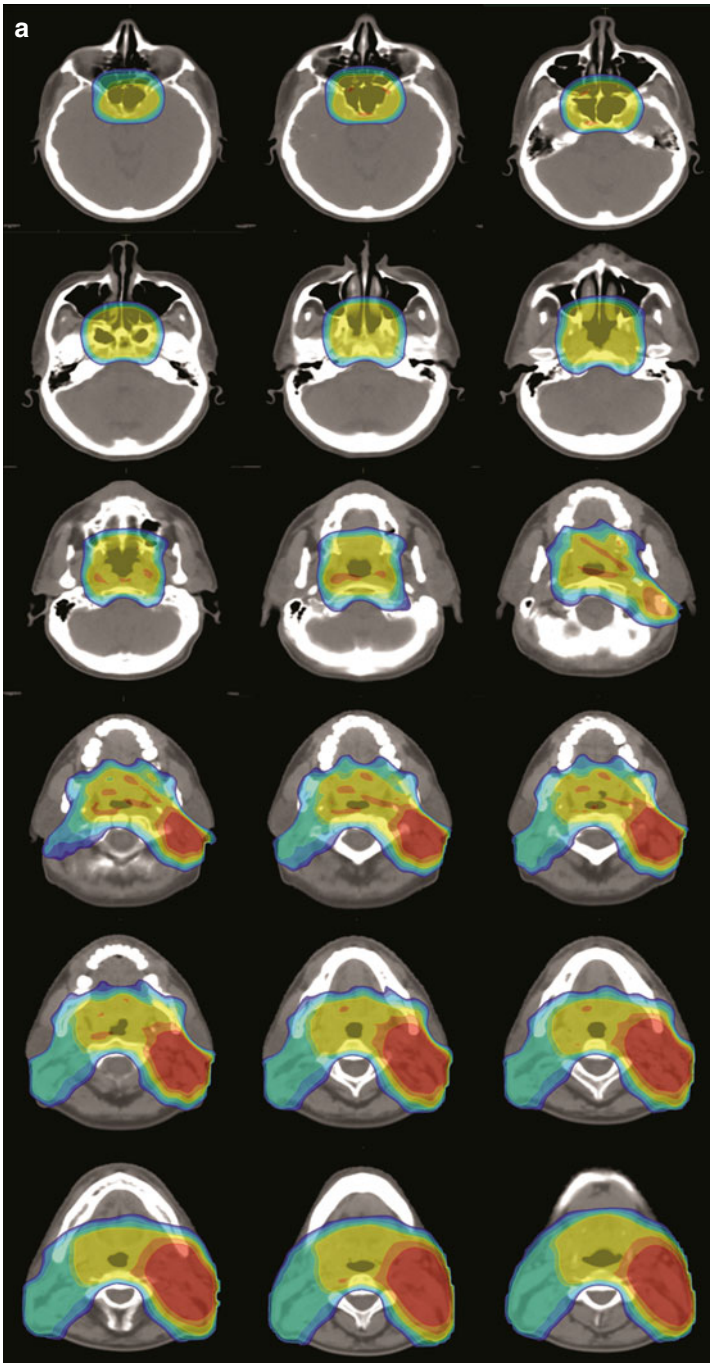

Fig. 11.3 Dose distribution of PTV70, PTV59.4, and PTV 54 Gy for the case presented here (**a**, **b**)

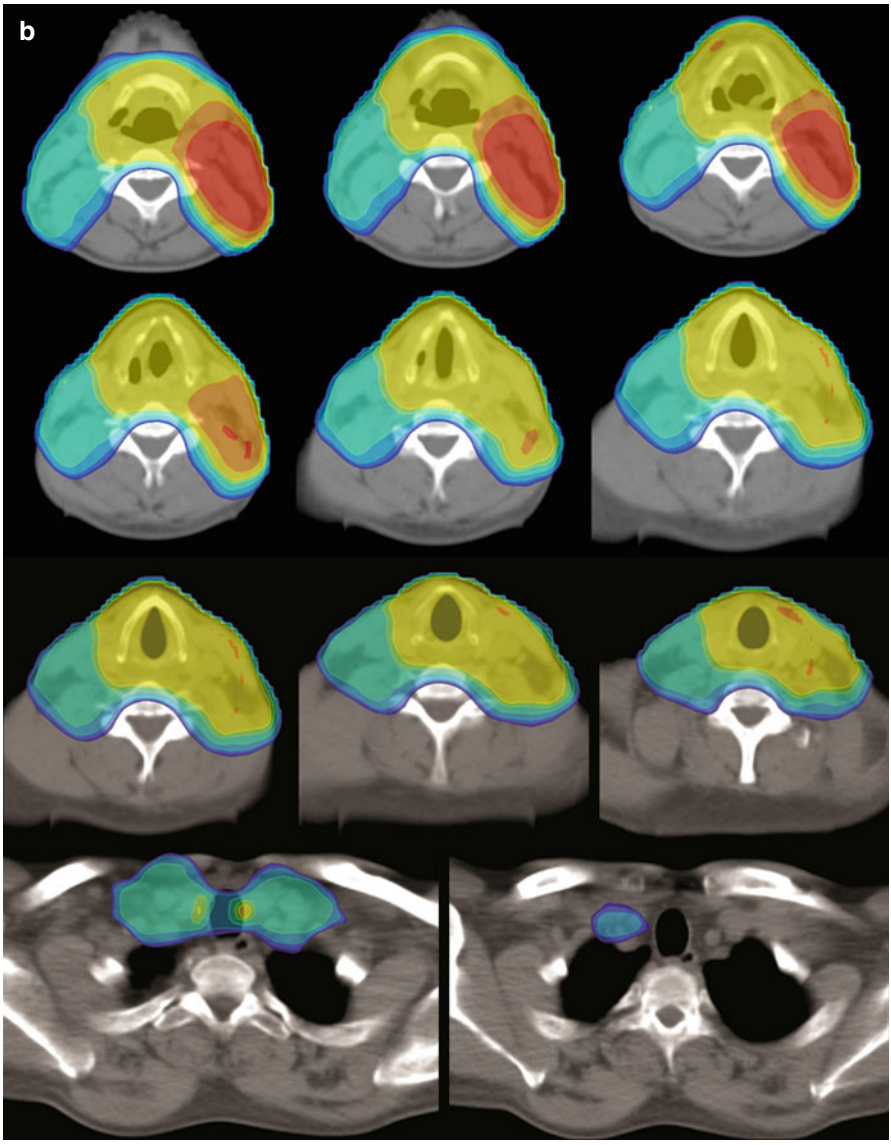

Fig. 11.3 (continued)

- *Mucosal Sites:* Depending on the field size, putative mucosal sites should receive 50–66 Gy (2 Gy/fr) with standard 3D-RT or sequentially planned IMRT. For highly suspicious mucosal sites, 60–66 Gy should be considered. If dose-painting IMRT or simultaneous integrated boost IMRT is utilized, doses of 54–66 Gy (1.63–2 Gy/fr in 33 fractions) are recommended as indicated.

Table 11.5 Recommendations for RT doses and fractionation for target volumes with standard or simultaneous integrated boost IMRT

Treatment type	PTV1	PTV2	PTV3
Definitive RT	66–70 Gy (2–2.12 Gy/fr)	59.4–66 Gy (1.8–2 Gy/fr)	46–54 Gy (1.63–2 Gy)
Definitive CRT	66–70 Gy (2–2.12 Gy/fr)	59.4–66 Gy (1.8–2 Gy/fr)	46–54 Gy (1.63–2 Gy)
Postoperative RT			
Risk factors (+)	66–70 Gy (2–2.12 Gy/fr)	59.4–66 Gy (1.8–2 Gy/fr)	46–54 Gy (1.63–2 Gy)
Risk factors (–)	60–66 Gy (2–2.12 Gy/fr)	54–63 Gy (1.8–1.9 Gy/fr)	46–54 Gy (1.63–2 Gy)
Postoperative CRT			
Risk factors (+)	66–70 Gy (2–2.12 Gy/fr)	59.4–66 Gy (1.8–2 Gy/fr)	46-54 Gy (1.63–2 Gy)
Risk factors (–)	60–66 Gy (2–2.12 Gy/fr)	54–63 Gy (1.8–1.9 Gy/fr)	46–54 Gy (1.63–2 Gy)

Abbreviations: *CRT* chemoradiotherapy, *IMRT* intensity-modulated radiation therapy, *PTV* Planning target volume, *RT* radiotherapy

- *Low-Intermediate-Risk PTV:* All suspected sites of subclinical spread including the nasopharynx, base of tongue, tonsils, pyriform sinus, and bilateral neck nodes (levels I–V)
  - In cases of 3D-RT or sequentially planned IMRT: 44–50 Gy in 2 Gy daily fractions
  - If IMRT is dose painting or simultaneous integrated boost: 54–63 Gy in 1.6–1.8 Gy daily fractions

Postoperative Radiotherapy

- Radiotherapy should preferentially commence on ≤6 weeks of postoperative period.
- *High-Risk PTV:* Includes the surgical field with adverse factors such as ECE (+) and/or close/positive surgical margins. Typical dose is 59.4–66 Gy (1.8–2 Gy/fr) for patients with ECE (+) and/or close surgical margins with concurrent chemotherapy. For patients with positive surgical margins, a dose of 70 Gy (2 Gy/fr) is recommended for 3D-RT or standard IMRT. If dose-painting IMRT or simultaneous integrated boost IMRT is used, then the dose is 70 Gy in 2.12 Gy daily fractions.
- *Mucosal Sites:* Depending on the field size, putative mucosal sites should receive 50–66 Gy (2 Gy/fr) with standard 3D-RT or sequentially planned IMRT. For highly suspicious mucosal sites, 60–66 Gy should be considered. If dose-painting

IMRT or simultaneous integrated boost IMRT is utilized, doses of 54–66 Gy (1.63–2 Gy/fr in 33 fractions) are recommended as indicated.

- *Low-Intermediate-Risk PTV:* All suspected sites of subclinical spread including the nasopharynx, base of tongue, tonsils, pyriform sinus, and bilateral neck nodes (levels I–V)
  - In cases of 3D-RT or sequentially planned IMRT: 44–50 Gy in 2 Gy daily fractions
  - If IMRT is dose painting or simultaneous integrated boost: 54–63 Gy in 1.6–1.8 Gy daily fractions

Postoperative Chemoradiotherapy

- Radiotherapy should preferentially commence on ≤6 weeks of postoperative period.
- Single-agent cisplatin at 100 mg/m^2 every 3 weeks is recommended concurrently with RT. Weekly use of cisplatin may be an alternative for patients anticipated to hardly tolerate or intolerate standard cisplatin protocol.
- *High-Risk PTV:* Includes the surgical field with adverse factors such as ECE (+) and/or close/positive surgical margins. Typical dose is 59.4–66 Gy (1.8–2 Gy/fr) for patients with ECE (+) and/or close surgical margins. For patients with positive surgical margins, a dose of 70 Gy (2 Gy/fr) is recommended for 3D-RT or standard IMRT. If dose-painting IMRT or simultaneous integrated boost IMRT is used, then the dose is 70 Gy in 2.12 Gy daily fractions.
- *Mucosal Sites:* Depending on the field size, putative mucosal sites should receive 50–66 Gy (2 Gy/fr) with standard 3D-RT or sequentially planned IMRT. For highly suspicious mucosal sites, 60–66 Gy should be considered. If dose-painting IMRT or simultaneous integrated boost IMRT is utilized, doses of 54–66 Gy (1.63–2 Gy/fr in 33 fractions) are recommended as indicated.
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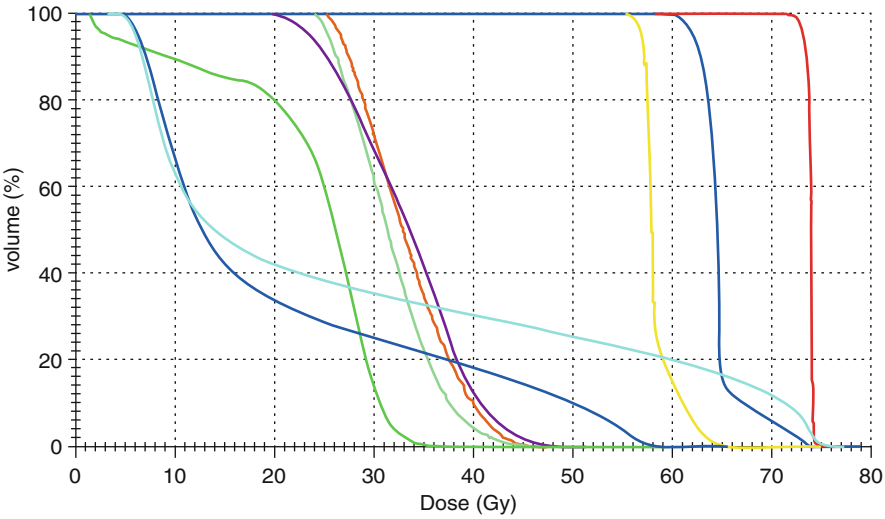
  - In cases of 3D-RT or sequentially planned IMRT: 44–50 Gy in 2 Gy daily fractions
  - If IMRT is dose painting or simultaneous integrated boost: 54–63 Gy in 1.6–1.8 Gy daily fractions
- *Guidelines for Normal Tissue Constraints:* Normal tissue dose constraints detailed below should strictly be obeyed to prevent debilitating late toxicities. Dose-volume histogram of critical organ doses for the present representative patient is demonstrated in Fig. 11.4:
  - Parotid glands: mean dose (D_{mean}) of ≤26 Gy or less *(should be achieved in at least one gland)* or at least 20 cc of the combined volume of both glands should receive <20 Gy or at least 50 % of one parotid gland should receive <30 Gy.). Brain stem: maximum dose (D_{max}) ≤54 Gy



Structure	Min dose Gy	Max dose Gy	Mean dose Gy
PTV 70 Gv	70.380	77.190	73.927
PTV 59.4 Gy	57.432	75.109	64.792
PTV 54 Gy	53.757	69.981	58.517
R cochlea	25.266	47.010	33.433
L cochlea	23.981	45.967	31.804
Brain stem	19.766	53.927	33.338
Spinal cord	1.386	39.279	23.707
R parotid	4.657	59.359	20.770
L parotid	4.289	78.999	28.380

Fig. 11.4 Dose-volume histogram of prescribed target volume doses and critical organs at risk

- Spinal cord: D_{max} ≤45 Gy oral cavity: D_{mean} <30 to 35 Gy
- Brain: D_{max} ≤50 Gy and any large volume of brain should receive <30 Gy
- Optic nerve, optic chiasm: D_{max} <54 Gy
- Lens: D_{max} is 10 Gy, and <5Gy if achievable
- Mandible: D_{max} <69 Gy (hot spots >70Gy should be kept out of the mandible).
- Cochlea: no more than 5 % receives ≥55 Gy
- Glottic Larynx: D_{mean} <36–45 Gy, if not suspected as potential primary

Table 11.6 IMRT plan assessment specifications

PTV	No variation	Minor variation
PTV_{70}	1. 95 % of any PTV_{70} is at or above 70 Gy 2. 99 % of PTV_{70} is at or above 65.1 Gy 3. No more than 20 % of PTV_{70} is at or above 77 Gy 4. No more than 5 % of PTV_{70} is at or above 80 Gy 5. Mean dose ≤74 Gy	1. 95 % of PTV_{70} is at or above 70 Gy 2. 97 % of PTV_{70} is at or above 65.1 Gy 3. No more than 40 % of PTV_{70} is at or above 77 Gy 4. No more than 20 % of PTV_{70} is at or above 80 Gy 5. Mean dose ≤76 Gy
PTV_{63} (if applicable)	1. 95 % of any PTV_{63} is at or above 63 Gy	1. 95 % of any PTV_{63} is at or above 58.6 Gy
	2. 99 % of PTV_{63} is at or above 58.6 Gy 3. No more than 20 % of PTV_{63} is at or above 77 Gy 4. No more than 5 % of PTV_{63} is at or above 80 Gy	2. No more than 40 % of PTV_{63} is at or above 77 Gy 3. No more than 20 % of PTV_{63} is at or above 80 Gy
$PTV_{59.4}$	1. 95 % of any $PTV_{59.4}$ is at or above 59.4 Gy 2. 99 % of $PTV_{59.4}$ is at or above 55.2 Gy	1. 95 % of $PTV_{59.4}$ is at or above 55.2 Gy 2. No more than 40 % of $PTV_{59.4}$ is at or above 77 Gy
	3. No more than 20 % of $PTV_{59.4}$ is at or above 77 Gy 4. No more than 5 % of $PTV_{59.4}$ is at or above 80 Gy	3. No more than 20 % of $PTV_{59.4}$ is at or above 80 Gy
PTV_{54} (if applicable)	1. 95 % of any PTV_{54} is at/or above 54 Gy 2. 99 % of PTV_{54} is at or above 50.2 Gy 3. No more than 20 % of PTV_{54} is at or above 65.3 Gy 4. No more than 5 % of PTV_{54} is at or above 68.3 Gy	1. 95 % of PTV_{54} is at or above 50.2 Gy 2. No more than 40 % of PTV_{54} is at or above 65.3 Gy 3. No more than 20 % of PTV_{54} is at or above 68.3 Gy

Abbreviations: IMRT intensity-modulated radiation therapy, *PTV* planning target volume (subscript denotes for prescribed dose)

– *Treatment Planning AssessmentStep 1:* Check whether the targets are adequately covered. As a common example recommended assessment specifications in Table 11.6 are given for typical dose prescriptions of PTV1 (PTV_{70}), PTV2 ($PTV_{59.4}$), and PTV3 (PTV_{54}). However, as various scenarios of patient presentation are possible (definitive RT, definitive CRT, postoperative RT with/without adverse factors, and postoperative CRT with/without adverse factors), all dose coverage values presented in percentages should also be used for any prescribed dose levels. All plans

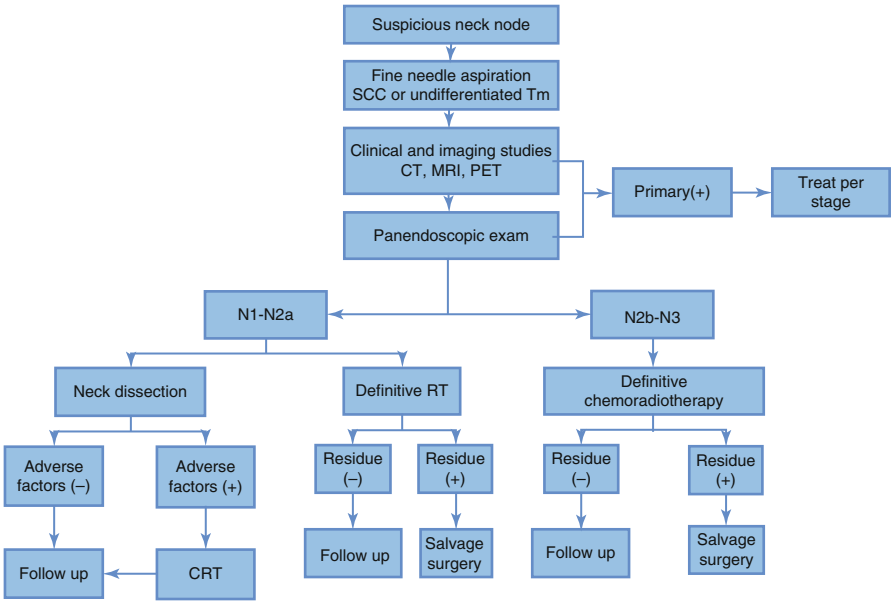


Fig. 11.5 Recommended algorithm for treatment of metastatic cervical cancer of occult primary

should be normalized to at least 95 % of the volumes of PTV1, PTV2, and PTV3 are covered by the 100 % of respectively prescribed isodose surfaces and 99 % of each PTV should be covered by 93 % of prescribed doses.

– Minor deviations are acceptable only for few assessment points where critical organ tolerance doses limit achieve excellent target coverage.
  – *Step 2:* Presence of a large hot spot should be carefully checked and should not be permitted for more than 20 % of PTV1 (e.g. 70 Gy) to receive ≥110 % and no more than 5 % of PTV1 to receive ≥%115 of prescribed dose, respectively.
  – *Step 3:* Normal tissue constraints should carefully be checked.
  – *Step 4:* Plan should be checked slide by slide via examining the isodose distribution to prevent the hot and cold spots not to exist on critical organs.
  – *Step 5:* Hot spots should be restricted to the GTV with being sure that the hot spot does not coincide on any nerve in the CTV.

- *Case Plan:* The patient with locally advanced MCCUP presented here was treated with concurrent CRT (cisplatin 100 mg/m^2, every 21 days) utilizing SIB-IMRT technique. As demonstrated in Figs. 11.2, 11.3 and 11.4, the prescribed doses for PTV1, PTV2, and PTV3 were 70, 59.4, and 54 Gy in 33 fractions, respectively.
- *Treatment Algorithm and Patient Follow-Up:* Recommended evidence-based treatment options and patient follow-up after treatment for MCCUP patients are as depicted in Figs. 11.5 and 11.6, respectively.

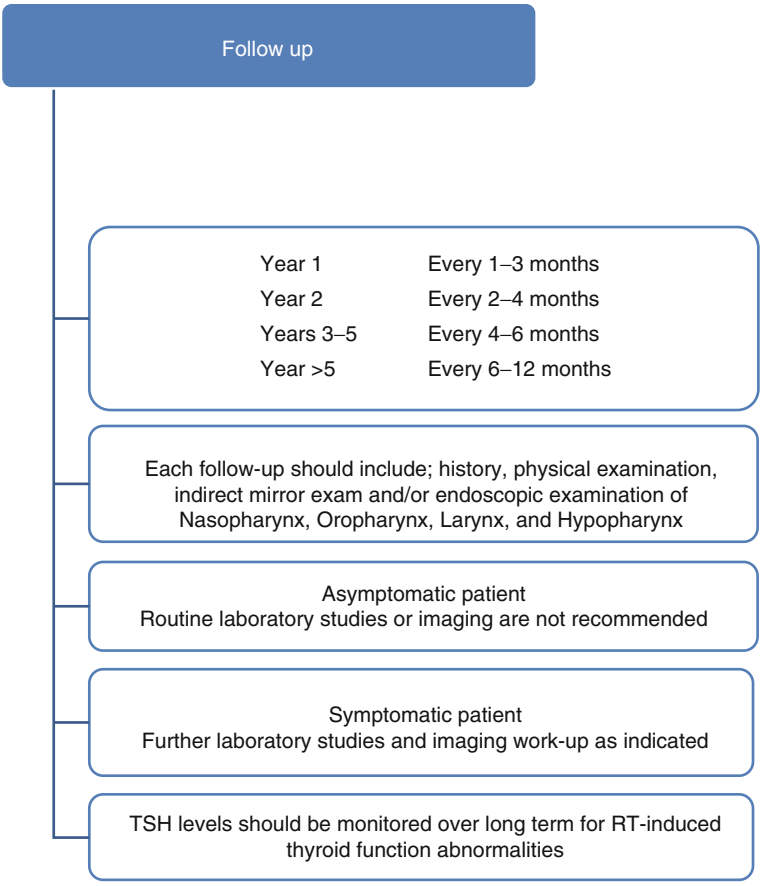


Fig. 11.6 Recommended algorithm for follow-up of metastatic cervical cancer of occult primary

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