Chemotherapy

13

Iwai Tohnai and Kenji Mitsudo

Abstract

For patients with locally advanced head and neck cancer, including in the oral cavity, surgery with or without radiotherapy is widely accepted as the standard treatment and is thought to be the most effective curative therapy. However, extended surgery causes loss of oral function, including swallowing and speech, and reduces patient's quality of life. To preserve function while maintaining or improving locoregional control and survival rates, concurrent chemoradiotherapy represents one of the standard treatment modalities for definitive treatment of locoregionally advanced squamous cell carcinoma of the oral cavity, particularly in resectable advanced cases. Retrograde superselective intra-arterial chemotherapy and daily concurrent radiotherapy have the advantage of delivering a high concentration of the chemotherapeutic agents to the tumor bed, and they can be used to provide daily concurrent chemoradiotherapy to patients with advanced oral cancer. The treatment results of retrograde superselective intra-arterial chemoradiotherapy for locally advanced oral cancer have been reported to be similar to those of surgery, suggesting the usefulness of this treatment modality.

Oral cancer patients with advanced cervical lymph node metastases have a poor prognosis. Hyperthermia has generally been confined to treatment of cervical lymph node metastases accessible with a radiofrequency system using external application and in combination with synergistic chemoradiotherapy. Thermochemoradiotherapy using retrograde superselective intra-arterial infusion is used in patients with advanced cervical lymph node metastases, and not only the primary lesion but also cervical lymph node metastases are controlled.

In this chapter, the therapeutic results in patients with advanced oral cancer treated with retrograde superselective intra-arterial chemoradiotherapy and the effectiveness of thermochemoradiotherapy for patients with advanced cervical lymph node metastases are described.

Keywords

Chemoradiotherapy • Hyperthermia • Oral cancer • Organ preservation • Retrograde superselective intra-arterial infusion

13.1 Introduction

Radical surgery for patients with locally advanced oral cancer causes various dysfunctions such as dysmasesis, speech disorders, and dysphagia. Furthermore, the cosmetic result after surgery is of greater concern than with other cancers, such as gastric cancer and lung cancer. Therefore, organ preservation without surgery is desired for patients with

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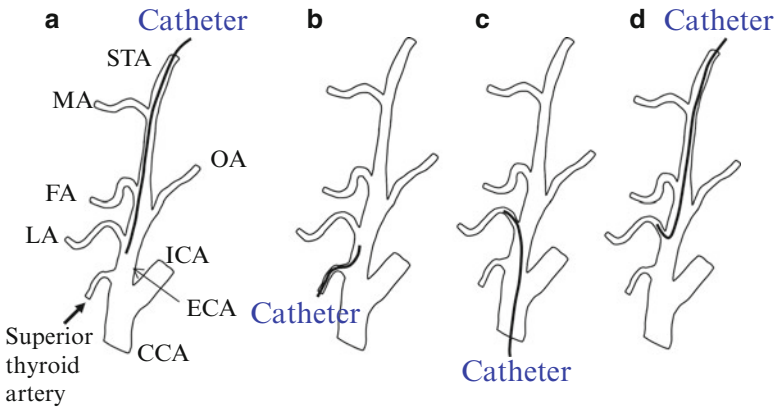


Fig. 13.1 The catheterization method for intra-arterial infusion. (**a**, **b**) Catheterization into ECA near a tumor-feeding artery via STA (**a**) or a superior thyroid artery (**b**) with a straight catheter. (**c**) Catheterization into the tumor-feeding artery via a femoral artery using the Seldinger method. (**d**) Catheterization into the tumor-feeding artery via STA with a hook-shaped catheter. *CCA* common carotid artery, *ICA* internal carotid artery, *ECA* external carotid artery, *LA* lingual artery, *FA* facial artery, *OA* occipital artery, *MA* maxillary artery, *STA* superficial temporal artery

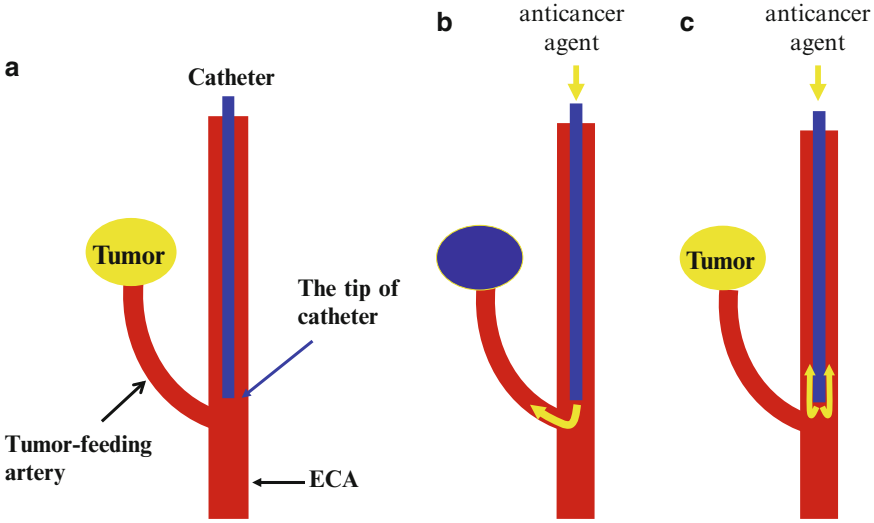


Fig. 13.2 (**a**) The tip of a straight catheter is located slightly peripheral to tumor-feeding artery. (**b**) The anticancer agents can be administered to the tumor with a manual one-shot injection of high pressure. (**c**) Anticancer agents cannot be administered to the tumor when a syringe pump is used because of low pressure

advanced oral cancer. One of the strategies of organ preservation therapy for advanced oral cancer patients is intra-arterial chemotherapy combined with radiotherapy.

Intra-arterial chemoradiotherapy (CRT) for head and neck cancer is historically classified into the following three groups. The oldest method is catheterization into the external carotid artery (ECA) near a target tumor-feeding artery via a superficial temporal artery (STA) or a superior thyroid artery using a straight catheter (Fig. 13.1a, b). The next method is catheterization into the tumor-feeding artery via a femoral artery using the Seldinger method (Fig. 13.1c). Superselective intra-arterial CRT using this method was found to be a beneficial treatment for advanced head and neck cancer. The third method is catheterization into the tumor-feeding artery via STA using a hook-shaped catheter (Fig. 13.1d). Superselective intra-arterial infusion using this method can be used to provide daily concurrent radiotherapy and chemotherapy for patients with advanced head and neck cancer, and it can be given safely without major complications, such as cerebral infarction. Intra-arterial chemotherapy for oral cancer using the three catheterization approaches is described below.

13.2 Conventional Intra-arterial Infusion via STA or a Superior Thyroid Artery (Catheterization into ECA)

Intra-arterial chemotherapy for head and neck cancer was first reported by Klopp et al. [1] and Sullivan et al. [2] in the 1950s. They reported insertion of a straight catheter into ECA via STA or a superior thyroid artery (Fig. 13.1a, b). The efficacy of treatment with intra-arterial chemotherapy has been reported [3–6].

Flow of the anticancer agents to the tumor bed is unstable with this method, because the tip of the catheter may be easily displaced near the tumor-feeding artery in ECA by neck extension. The tip of a straight catheter is located slightly peripheral to the tumor-feeding artery in ECA (Fig. 13.2a), and the anticancer agents can be administered to the tumor with a manual one-shot injection of high pressure (Fig. 13.2b). On the other hand, anticancer agents cannot be administered to the tumor when a syringe pump is used because of low pressure (Fig. 13.2c).

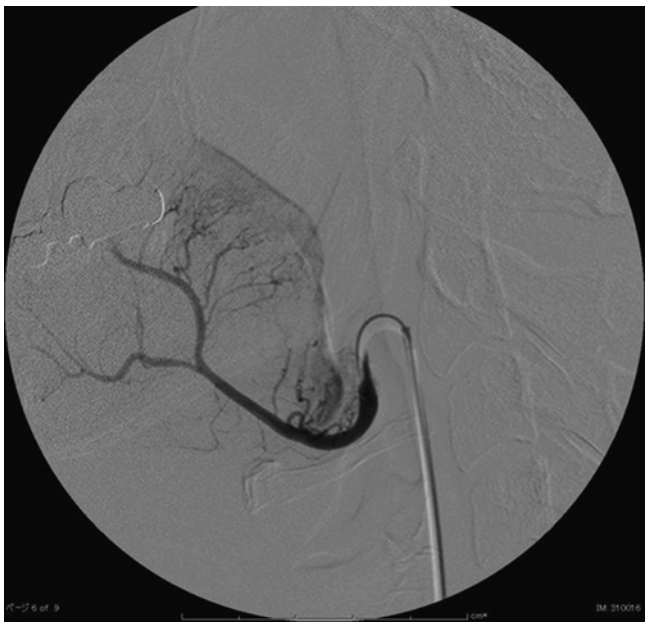


Fig. 13.3 Superselective intra-arterial infusion via a femoral artery by the Seldinger method. Tumor staining of the tongue from LA can be seen with use of contrast medium on digital subtraction angiography (DSA) (this figure was sponsored by Dr. Takamatsu S. at Fukui Prefectural Hospital)

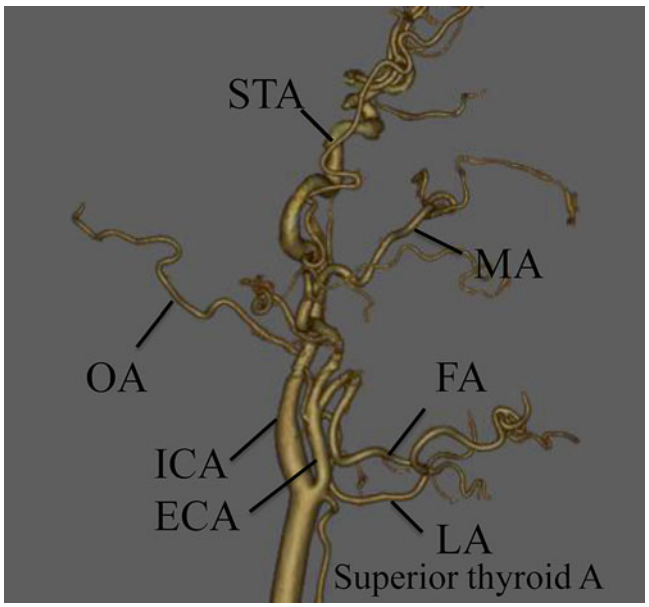


Fig. 13.4 Three-dimensional computed tomography angiography (3D-CTA) of the carotid artery

13.3 Superselective Intra-arterial Infusion via a Femoral Artery by the Seldinger Method

Lee et al. [7, 8] first reported superselective intra-arterial chemotherapy via a femoral artery using the Seldinger method (Fig. 13.3), and Robbins et al. [9–11] have developed a cisplatin (CDDP) delivery system in which extremely large amounts of anticancer agent with radiotherapy can be administered to patients with advanced head and neck cancer. Given the acronym "RADPLAT," this consists of rapid superselective intra-arterial infusions combined with intravenous sodium thiosulfate for systemic CDDP neutralization. They conducted a phase I study designed to determine the maximum-tolerated dose of CDDP that could be administered in intra-arterial chemotherapy. The maximum-tolerated dose was 150 mg/m^2/week for 4 weeks. In addition, this method has been found highly useful in the treatment of cervical lymph node metastasis [12, 13]. There have been many reports of RADPLAT for head and neck cancer [14–20], and RADPLAT has been widely accepted worldwide. However, Rasch et al. [21] reported that the local control rate and the survival rate of RADPLAT were no different from those of intravenous CRT in the Netherlands. Robbins questioned whether the result of this randomized trial was related to the technique used to deliver the intra-arterial infusions [22].

Catheterization via a femoral artery using the Seldinger method sometimes causes serious problems, such as cerebral infarction and sudden death [7, 8]. There is an interesting report that institutions inexperienced in the use of RADPLAT had a higher rate of grades 4 and 5 toxicities related to cerebral infarction than experienced institutions did [17].

13.4 Superselective Intra-arterial Infusion via STA and an Occipital Artery (OA)

This method was developed to overcome the disadvantages associated with the techniques mentioned above. A hook-shaped catheter is inserted from STA in retrograde fashion into a tumor-feeding artery; the usefulness of this method in combination with radiotherapy has been reported [23–27].

Before treatment, 3-dimensional computed tomography angiography (3D-CTA) of the carotid artery is necessary to identify the main tumor-feeding arteries and determine the morphology of the tumor-feeding artery originating from ECA (Fig. 13.4). Patients with severe calcification of the carotid artery or stenosis of the internal/external carotid artery are ineligible (Fig. 13.5a, b).

Catheterization from STA is performed according to the method of Hattori, Fuwa and Tohnai [23–25] (HFT method) [28] (Figs. 13.6, 13.7, and 13.8). STA is exposed by a 30-mm skin incision in the preauricular region of the affected side (Fig. 13.7a, b). Indwelling needle is inserted into STA (Fig. 13.7c), and an inner needle is removed from an outer needle A 0.016-inch guidewire (GT wire, Terumo Corp., Tokyo,

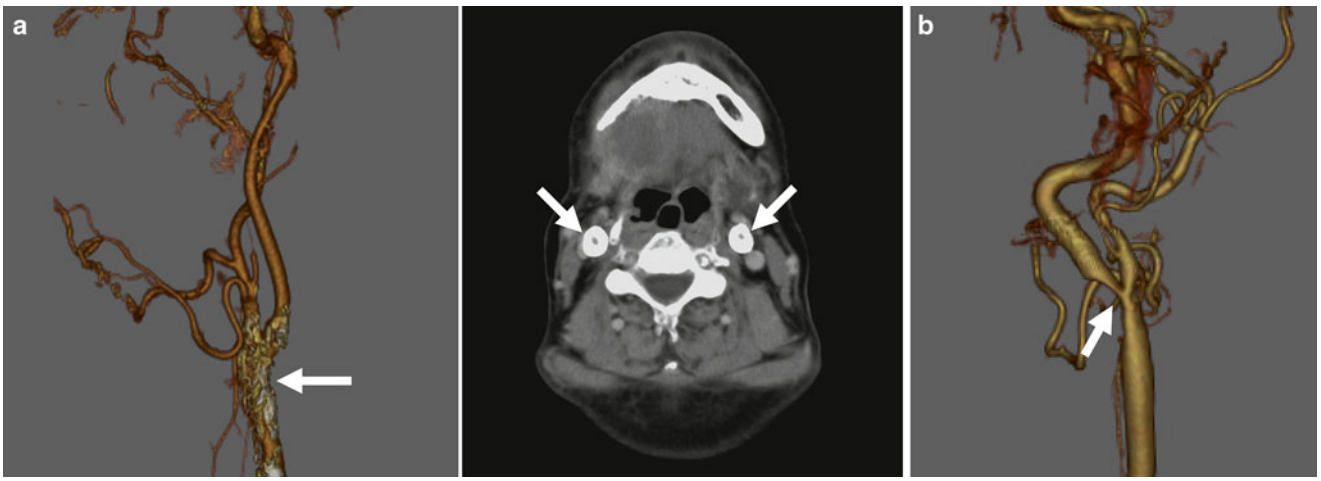


Fig. 13.5 Calcification of the external carotid artery (**a**: *arrowhead*) and stenosis of the internal carotid artery (**b**: *arrowhead*). Catheter insertion is contraindicated in these cases

Japan) (Fig. 13.6a) is inserted into the common carotid artery through an outer needle (Fig. 13.7d). A vinyl hook-shaped catheter (NECK, 4 Fr in outer diameter, Medikit Corp., Tokyo, Japan) (Fig. 13.6b) is inserted into STA along the guidewire (Fig. 13.7e) and placed below the bifurcation of the target artery (Fig. 13.7f). The tip of the catheter is then superselectively inserted into the target artery by drawing it back under fluoroscopic guidance (Fig. 13.7g, h), and the position of the catheter is checked by injection of contrast medium and blue dye (Fig. 13.7i, j). When catheterization using a hook-shaped catheter is not stable, the guidewire exchange method is used to replace it with a polyurethane straight catheter (Fig. 13.6c) [29].

When the tumor has two or more feeding arteries, catheters are inserted into the two arteries via STA and OA or bilaterally. Catheterization from OA is performed according to the method of Iwai et al. [30] (Fig. 13.8). OA is identified posterior of the mastoid process by an ultrasonic blood flow detector (Doppler ultrasound) (13.7d, and Fig. 13.8a). A 35-mm skin incision is made, and the sternocleidomastoid muscle and splenius capitis muscle are safely transected using the ultrasonic scalpel without OA injury (Fig. 13.7e, and 13.8b–e). Then, the catheter is superselectively inserted into the target artery under fluoroscopic guidance. The transected muscles, subcutaneous tissues, and skin are sutured, and the catheter is fixed to the skin around the mastoid process.

After catheterization, flow-check digital subtraction angiography (DSA) and angio-CT are performed in all cases (Fig. 13.9a–d). Angio-CT is helpful for detecting tumors by confirming the enhancement of the feeding area and for enabling the catheter to be placed at the appropriate position. Furthermore, weekly confirmation of the feeding artery by injection of a small amount of indigo carmine is important (Fig. 13.9e, f).

13.5 Radiotherapy

Radiotherapy is planned for all patients after appropriate immobilization using a thermoplastic mask and three-dimensional CT-based techniques. Conventional radiotherapy is performed with 4 or 6 MV at 2 Gy/fr/day. The irradiation field is changed according to lymph node status. In cases of N0 disease, the field contains the primary site and levels I–III of the neck on the ipsilateral side. The dose is delivered to 40 Gy/20fr. The portal is then reduced to only the primary site to spare the spinal cord. The total dose delivered to the primary tumor is 60 Gy/30fr. In cases of N1, N2a, and N2b diseases, the field contains the primary site and levels I–V of the neck on the ipsilateral side. The dose is delivered at 40 Gy/20fr. The portal is then reduced to the primary site and lymph node metastases. The dose for the spinal cord ranges from 40 Gy to 45 Gy. The total dose delivered to the primary tumor is 60 Gy/30fr and that to the metastatic lymph node sites is to 50 Gy/25fr. In cases of N2c disease, the field contains the primary site and levels I–V of the neck on bilateral sides. The dose is delivered at 40 Gy/20fr. The portal is then reduced to the primary site and lymph node metastases. The dose to the spinal cord ranges from 40 Gy to 45 Gy. The total dose delivered to the

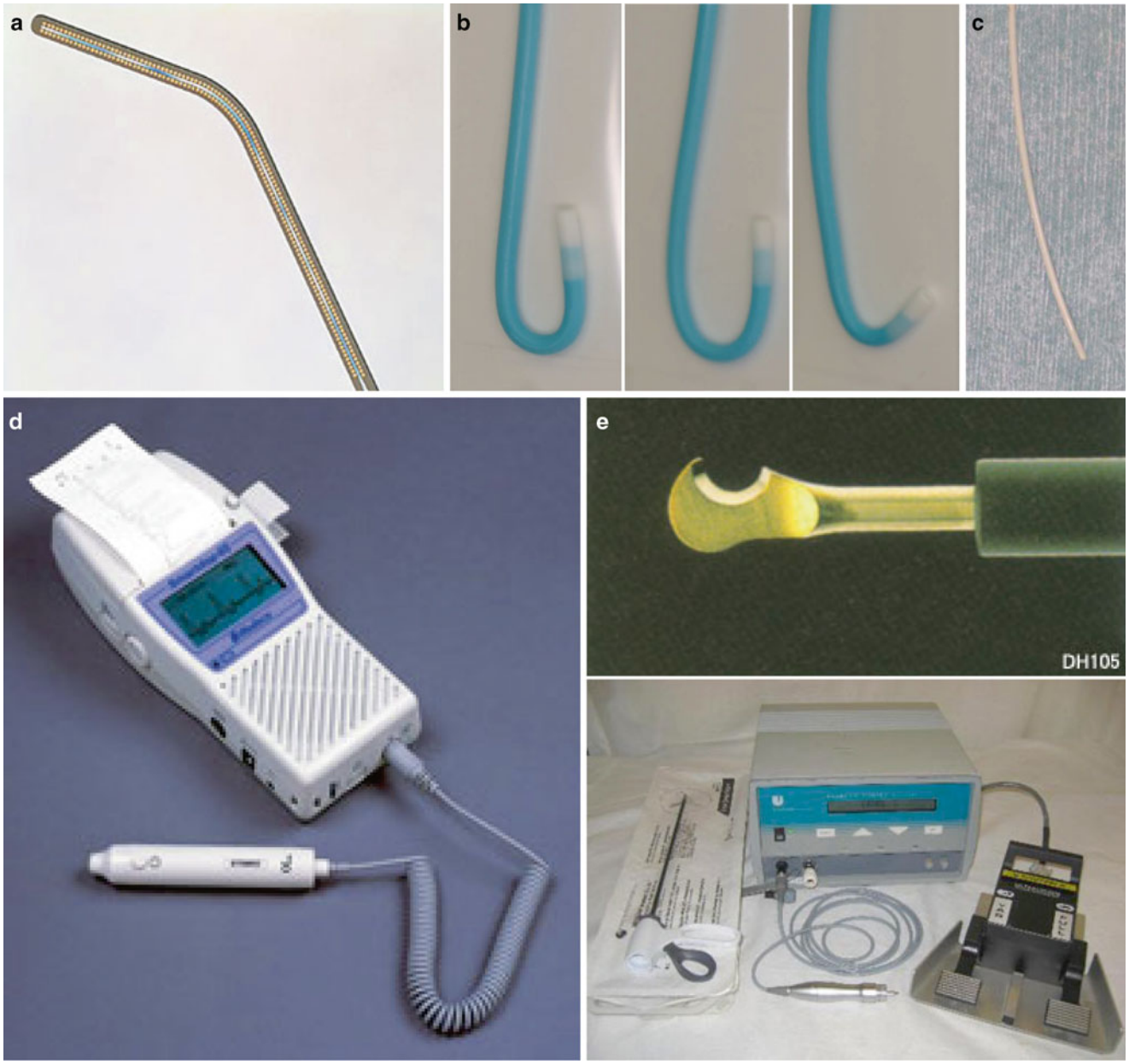


Fig. 13.6 (**a**) A 0.016-inch guidewire (Radifocus Guide Wire, Terumo Corp., Tokyo, Japan), (**b**) a hook-shaped catheter (Neck, Medikit Corp., Tokyo, Japan) (light, Neck 1G; *middle*, Neck 2G; *right*, Neck M), (**c**) a polyurethane straight catheter (Anthron P-U catheter, Toray Medical Co., Ltd., Tokyo, Japan), (**d**) ultrasonic blood flow detector (Smartdop 45, KDD Co, Ltd., Shiga, Japan), (**e**) electrosurgical diathermy (Harmonic scalpel, Johnson & Johnson K.K)

primary tumor is 60 Gy/30fr, and, if at all possible, the total dose delivered to the metastatic lymph node sites is 50 Gy/25fr.

13.6 Superselective Intra-arterial Chemoradiotherapy

The anticancer agent is injected in a bolus through the intra-arterial catheter when radiotherapy is performed. The total dose of docetaxel (DOC) is 60 mg/m^2 (10 mg/m^2/week) and that of CDDP is 150 mg/m^2 (5 mg/m^2/day) (Fig. 13.10). Sodium thiosulfate (1 g/m^2) is administered intravenously to provide effective CDDP neutralization after the anticancer agent is given. All patients are given a 5HT-3-receptor antagonist before administration of the anticancer agent.

13.7 Surgery

The purpose of this combined CRT using superselective intra-arterial infusion is to improve the local control rate and achieve good QOL without surgery. If there is residual primary tumor after this treatment or recurrence of the

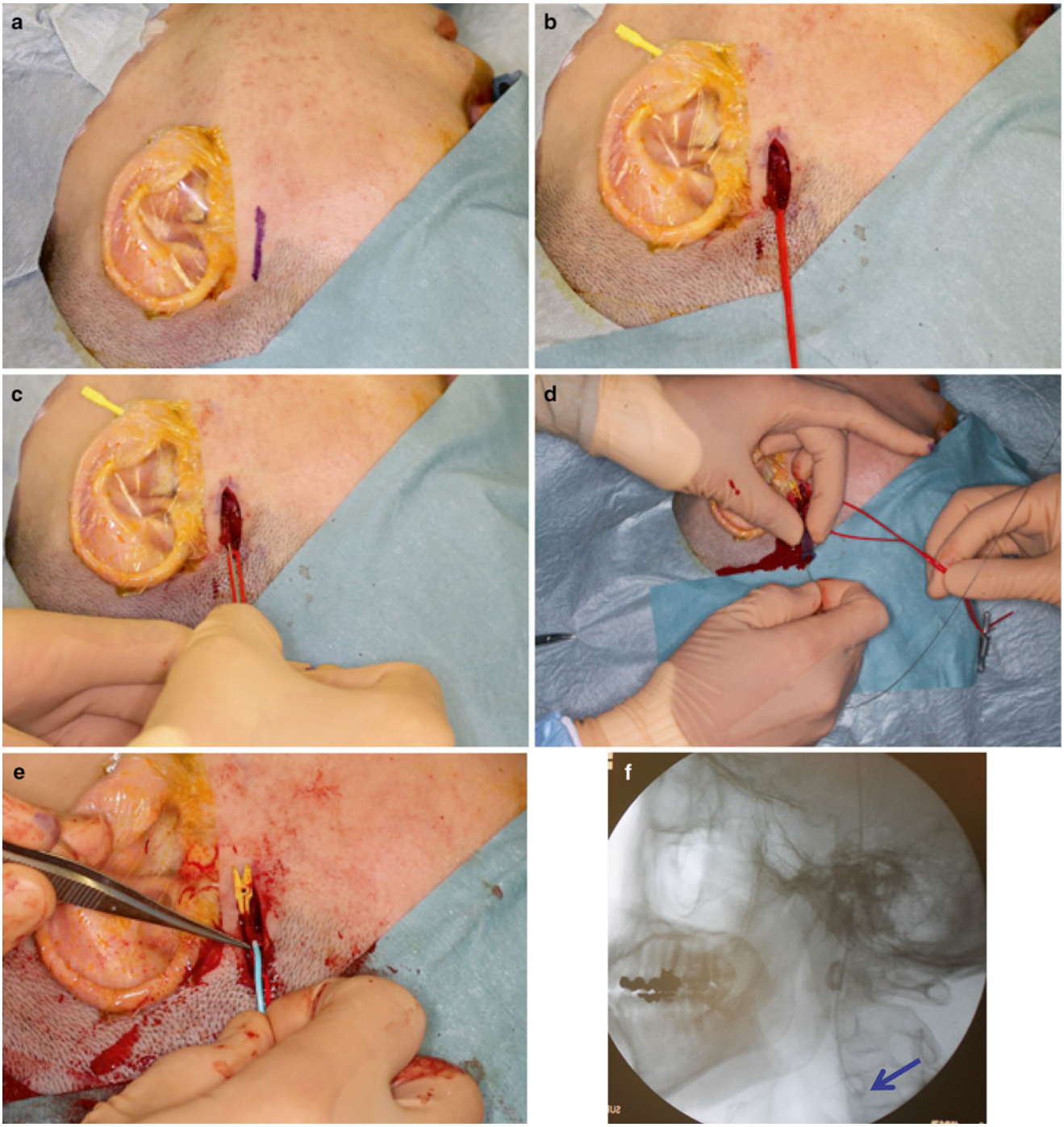


Fig. 13.7 STA is exposed by a 30-mm skin incision in the preauricular region (**a**, **b**). Indwelling needle is inserted into STA (**c**), and a guidewire is inserted into the common carotid artery (**d**). A hook-shaped catheter is inserted into STA along the guidewire (**e**) and placed below the bifurcation of the target artery (**f**, *arrowhead*). The tip of the catheter is then superselectively inserted into a target artery (**g**, facial artery, *arrowhead*) (**h**, maxillary artery, *arrowhead*). The position of the catheter is checked by injection of contrast medium and blue dye. Anterior and lower of the tumor is dyed from a facial artery (**i**, *arrowhead*), and posterior of the tumor is dyed from a maxillary artery (**j**, *arrowhead*).

primary lesion, salvage surgery is planned. In cases of cervical metastatic lymph nodes, the primary lesion is preserved and radical neck dissection is performed 5–6 weeks after the end of intra-arterial CRT.

13.8 Toxicity Assessment

Toxicities encountered during therapy are evaluated according to the National Cancer Institute—Common Terminology Criteria for Adverse Events v3.0.

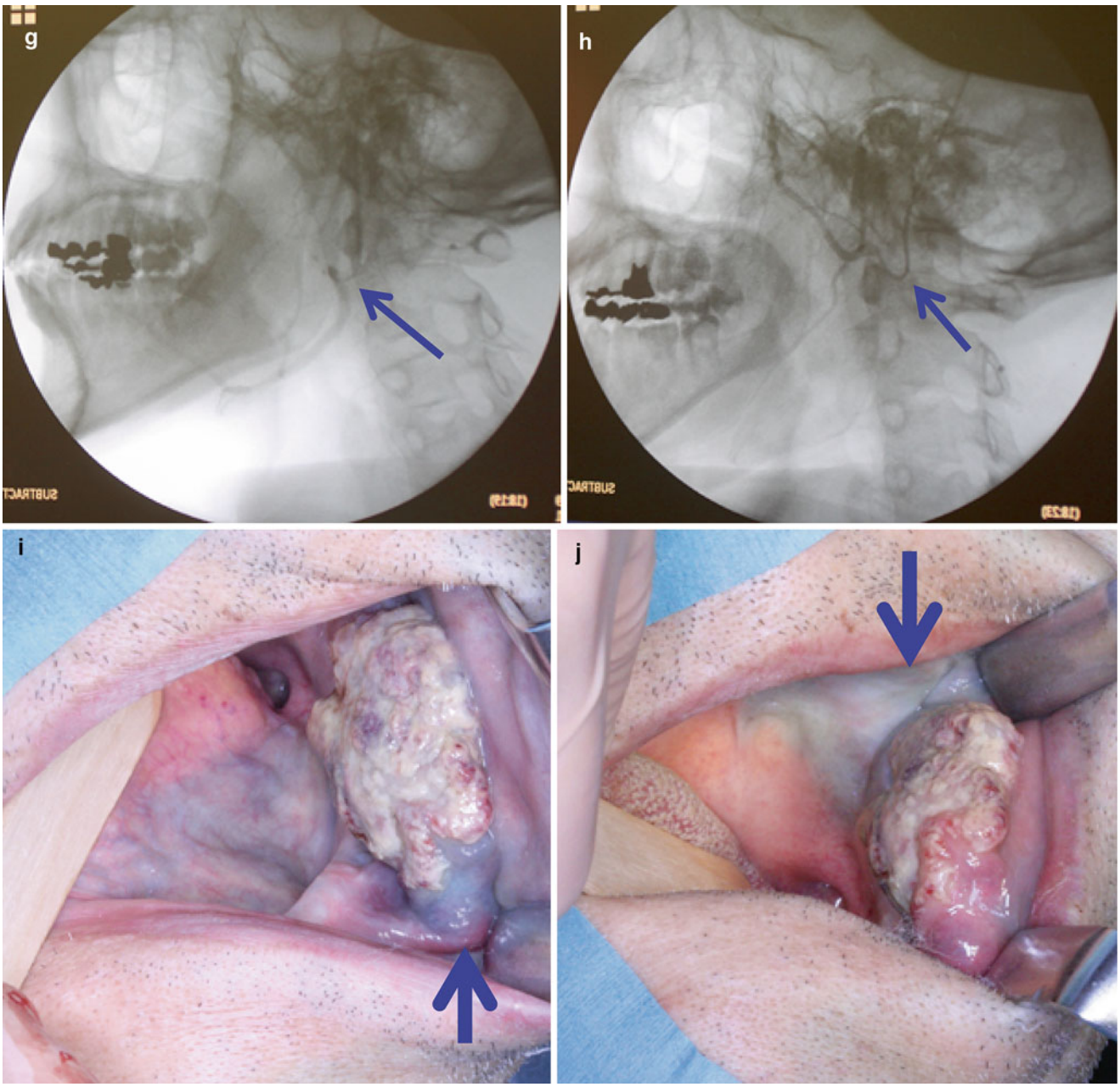


Fig. 13.7 (continued)

13.9 Results of Retrograde Superselective Intra-arterial CRT

One hundred and twelve patients with stages III and IV oral squamous cell carcinoma underwent retrograde intra-arterial chemoradiotherapy between August 2006 and July 2011. After intra-arterial CRT, the primary site complete response was achieved in 1998 (87.5 %) of 112 cases. Five-year survival and local control rates were 71.3 % and 79.3 %, respectively. Grade 3 or 4 toxicities included mucositis in 92.0 %, neutropenia in 30.4 %, dermatitis in 28.6 %, anemia in 26.8 %, and thrombocytopenia in 7.1 % of patients. Grade 3 toxicities included dysphagia in 72.3 %, nausea/vomiting in 21.4 %, fever in 8.0 %, and renal failure in 0.9 % of patients [31]. Retrograde superselective intra-arterial chemotherapy and daily concurrent radiotherapy for stages III and IV oral cancers provided good overall survival and local control. All patients had squamous cell carcinoma of the oral cavity in this study; this treatment has also been reported to be effective for sarcoma and adenoid cystic carcinoma of the head and neck [32, 33].

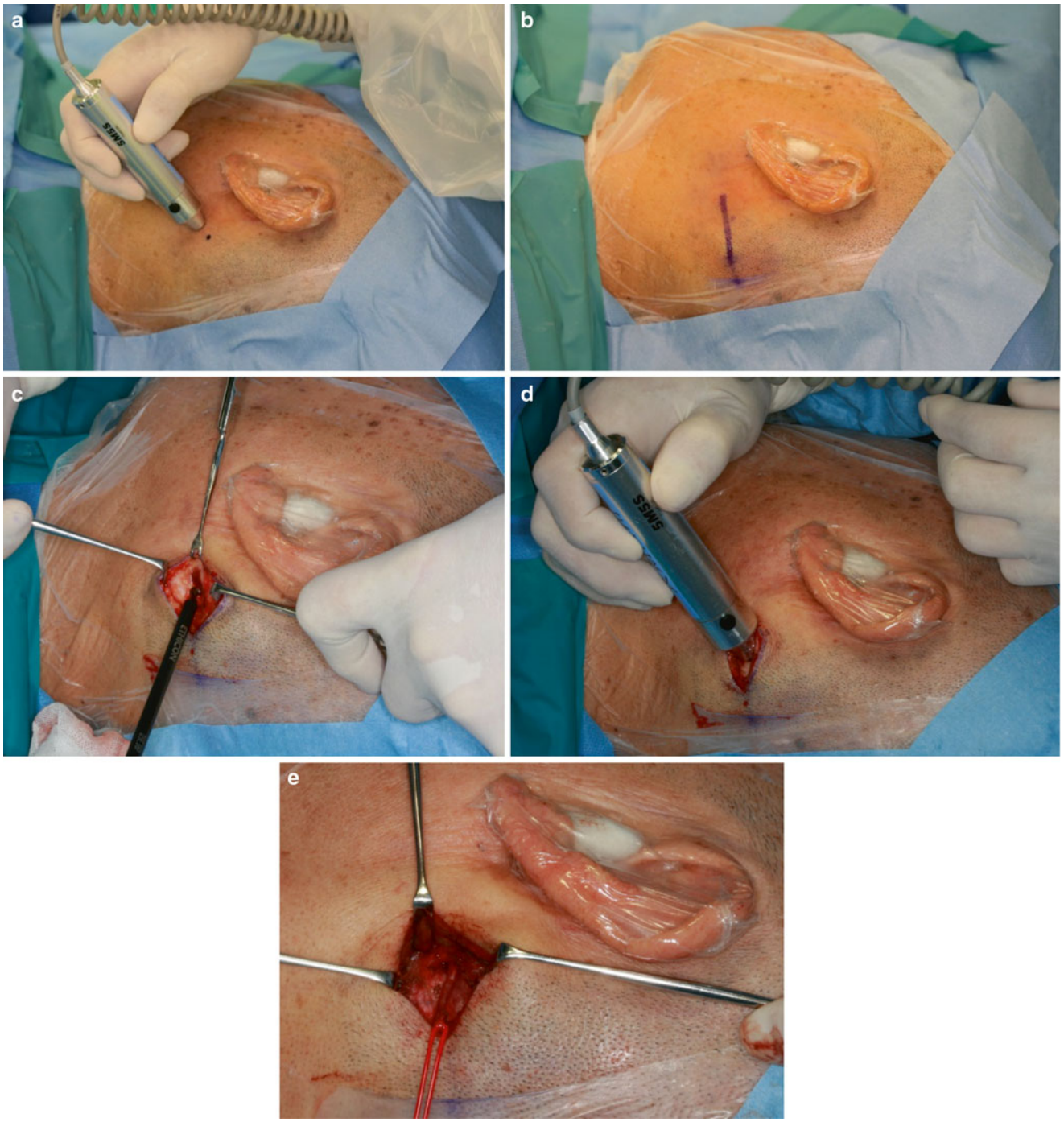


Fig. 13.8 OA is identified posterior of the mastoid process by an ultrasonic blood flow detector (**a**). A 35-mm skin incision is made (**b**), and the sternocleidomastoid muscle and splenius capitis muscle are safely transected using the ultrasonic scalpel (**c, d**), and OA is exposed (**e**). Then, the catheter is superselectively inserted into the target artery under fluoroscopic guidance

Case 1: Squamous cell carcinoma of the buccal mucosa (T3N0M0) (Fig. 13.11)

Superselective intra-arterial CRT (DOC total 60 mg/m^2; CDDP total 150 mg/m^2, total 60 Gy) was performed for 6 weeks. After completion of the treatment, pathological complete response was achieved at the primary site, and the patient has been free of disease for 5 years and 3 months.

13.10 Thermochemoradiotherapy

Patients with head and neck squamous cell carcinoma with advanced cervical metastases represent a treatment dilemma because their prognosis is generally considered to be poor. Especially when cervical lymph node metastases exceed 6 cm in their largest diameter (N3) or there are multiple

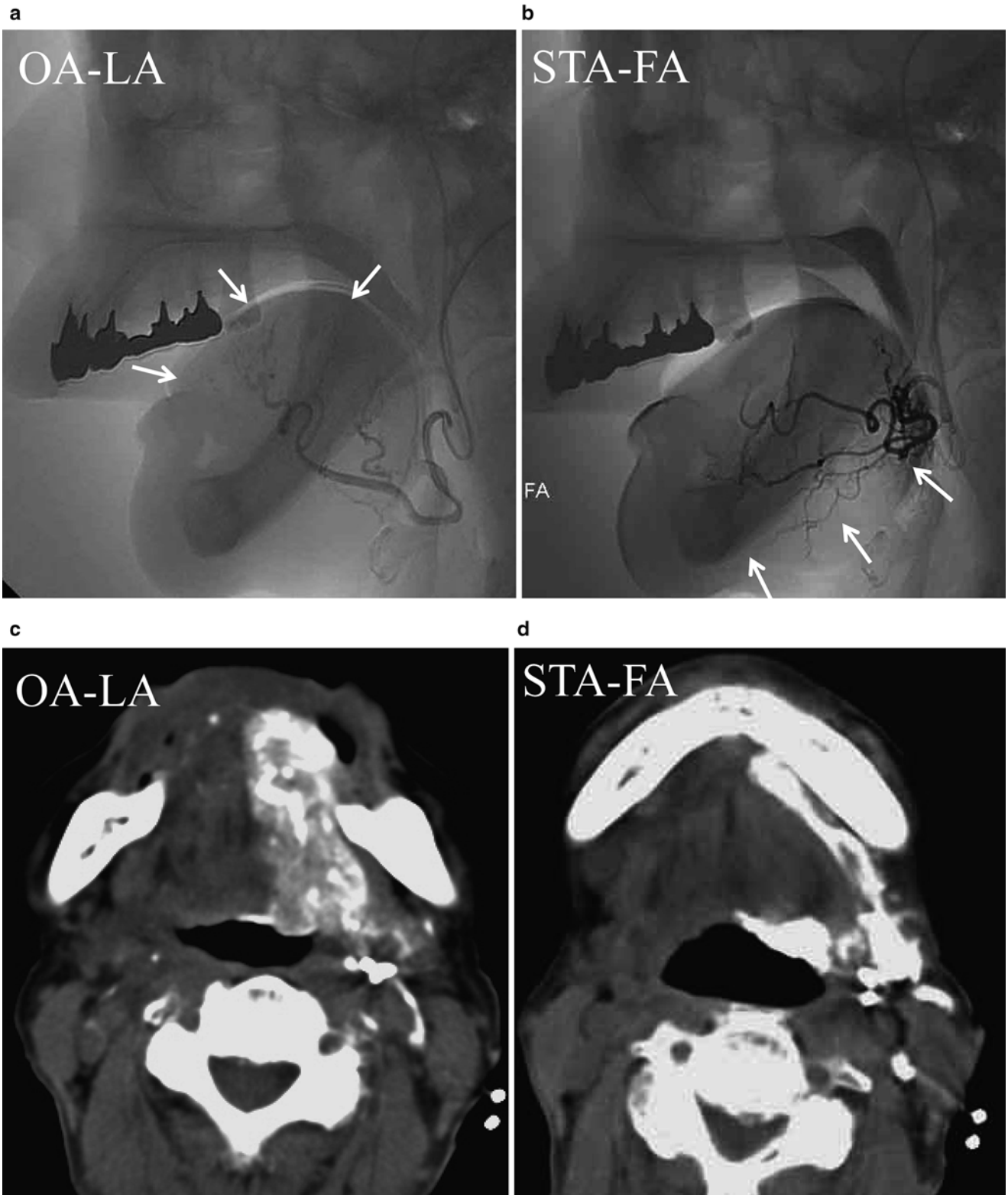
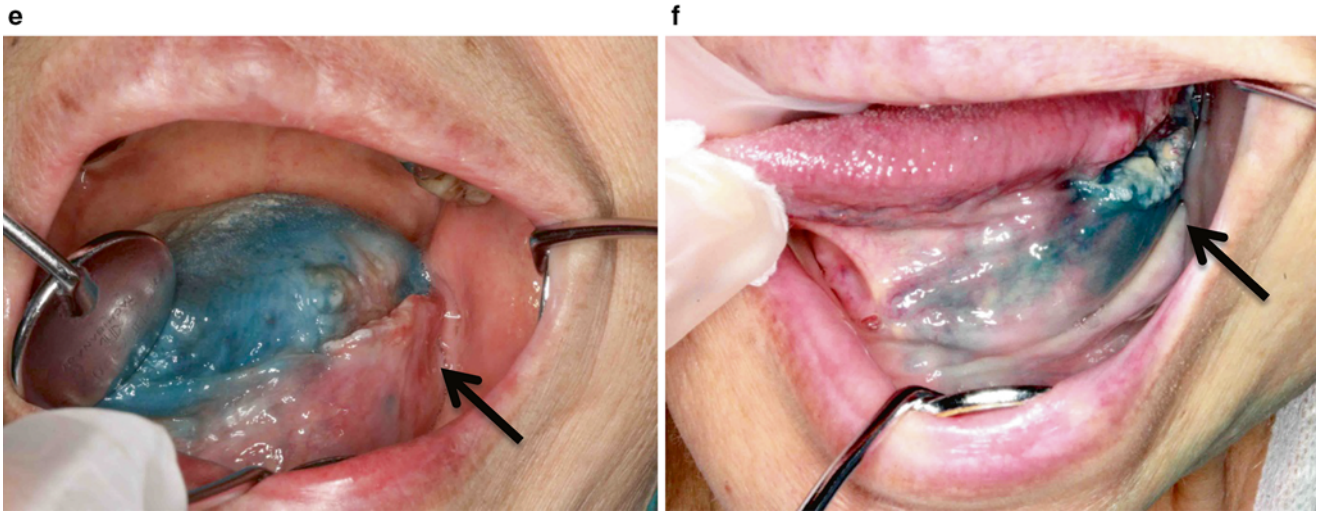


Fig. 13.9 Squamous cell carcinoma of the tongue (T3N1M0). (**a**, **b**) DSA of retrograde superselective intra-arterial infusion. Two catheters are superselectively inserted into left LA via OA (OA-LA) (**a**) and left FA via STA (STA-FA) (**b**). Tumor stain is seen with the use of contrast medium on flow-check DSA (*arrowhead*). (**c**, **d**) Axial views of angio-CT. Angio-CT images show that tumor staining of the left tongue from left LA (**c**) and the left mouth floor from left FA (**d**) can be seen with the use of contrast medium. (**e**, **f**) The left side of the tongue tumor extends to the floor of the mouth. The perfusion area from left LA is not visible to the floor of the mouth (**e**, *arrowhead*), and the perfusion area of the floor of the mouth and the inside of the mandible is seen from left FA (**f**, *arrowhead*)



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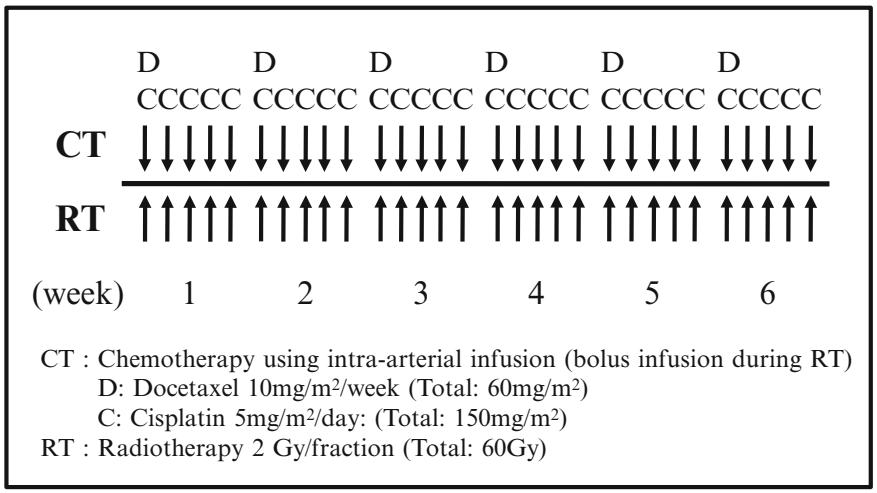

Fig. 13.10 Treatment schedule for chemoradiotherapy using intra-arterial infusion. External irradiation is performed 5 times a week at 2 Gy per fraction, to a total of 60 Gy, for 6 weeks. The anticancer agent is injected in a bolus through the intra-arterial catheter when radiotherapy is performed. The total dose of DOC is 60 mg/m^2 (15 mg/m^2/week), and that of CDDP is 150 mg/m^2 (5 mg/m^2/day)

lymph node metastases (N2b, 2c), treatment of these metastases is extremely difficult and is often associated with poor prognoses. The use of hyperthermia (HT) has generally been confined to cervical lymph node metastases accessible with a radiofrequency system employing external application and in combination with synergistic CRT.

13.11 Superselective Intra-arterial CRT Combined with HT

Our strategy for patients with advanced cervical metastases (N2 and N3) is to use thermochemoradiotherapy with retrograde superselective intra-arterial infusion. Treatment consists of superselective intra-arterial CRT (DOC total 60 mg/m^2; CDDP total 150 mg/m^2, total 60 Gy) and HT for 6 weeks. Radiofrequency capacitive heating equipment (8 MHz, maximum RF output of 60–1,500 W, Thermotron RF-8; Yamamoto Vinita Co. Ltd., Osaka, Japan) is used for HT. Two opposing 10-cm electrodes are generally used for heating the cervical lymph node metastases. The electrodes are covered with a water pad, and one is placed along the metastatic node, while the other is for the contralateral site (Fig. 13.12f). HT is applied once or twice per week and administered for 50 min within 30 min after each radiotherapy session.

13.12 Surgery After Thermochemoradiotherapy

The primary lesion and metastatic cervical lymph nodes are assessed 4 weeks after completion of all treatments. Patients are scheduled to undergo neck dissection 5–8 weeks after the end of thermochemoradiotherapy, unless distant

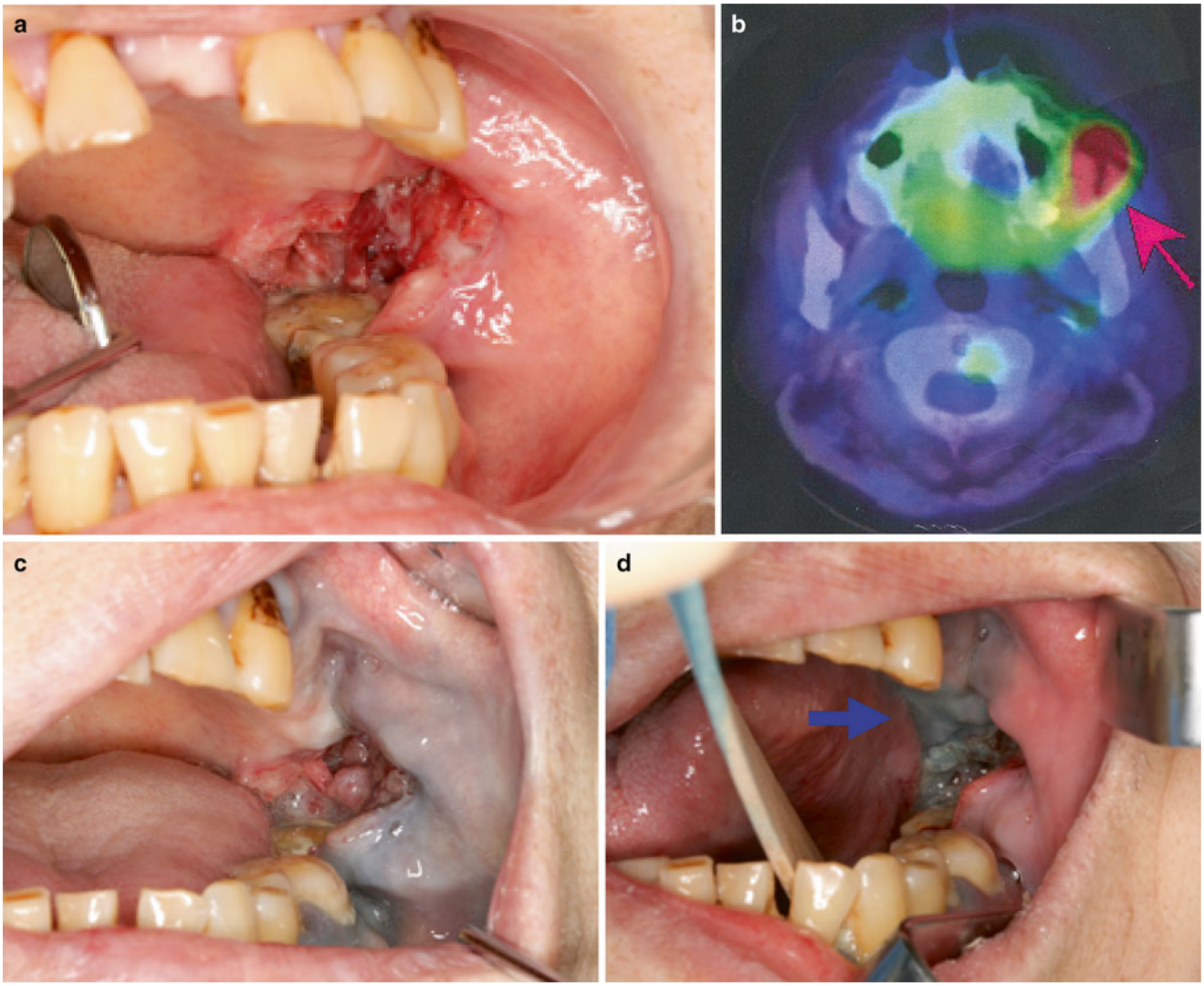

Fig. 13.11 Squamous cell carcinoma of the buccal mucosa (T3N0M0). Clinical findings reveal an ulcerated mass originating from the left buccal mucosa. The mass measures 42×32 mm and spreads to the upper and lower gingiva (**a**). Positron emission tomography–computed tomography (PET–CT) demonstrates high uptake of 18-fluorodeoxyglucose (FDG) at the left buccal mucosa (**b**, *arrowhead*). Two catheters are superselectively inserted into left FA and MA via left STA and OA. The perfusion area from the left FA is the buccal mucosa and the lower and upper gingiva (**c**). On the other hand, the perfusion area of the inside of the tumor, soft palate and anterior palatine arch, is seen from left MA (**d**, *arrowhead*). Tumor stain is seen with the use of contrast medium for the anterior side of the tumor (**e**, *arrowhead*) from FA and posterior side of the tumor (**f**, *arrowhead*) from MA. After the completion of treatment, the primary tumor has disappeared (**g**), and FDG uptake on PET–CT has disappeared (**h**)

metastases are found. If there is residual primary tumor after this treatment, salvage surgery involving both primary and cervical lymph nodes is performed.

13.13 Treatment Results of Thermochemoradiotherapy for Oral Cancer with N3 Cervical Lymph Node Metastases

We applied thermochemoradiotherapy using superselective intra-arterial infusion for patients with advanced cervical metastases and reported the treatment efficacy [34, 35, 36]. In our previous report, nine patients with N3 cervical lymph node metastases of oral squamous cell carcinoma underwent thermochemoradiotherapy using superselective intra-arterial infusion, and 5-year survival and locoregional control rates were 51 % and 88 %, respectively [34].

Case 2: Squamous cell carcinoma of the upper gingiva (T2N3M0) (Fig. 13.12)

Superselective intra-arterial CRT is combined with HT (DOC total 60 mg/m^2; CDDP total 150 mg/m^2, total 60 Gy, HT: 5 sessions) for 6 weeks. After the intra-arterial CRT is combined with HT, pathological complete response was achieved at the primary site. Radical neck dissection was carried out, and pathological complete response was recog-

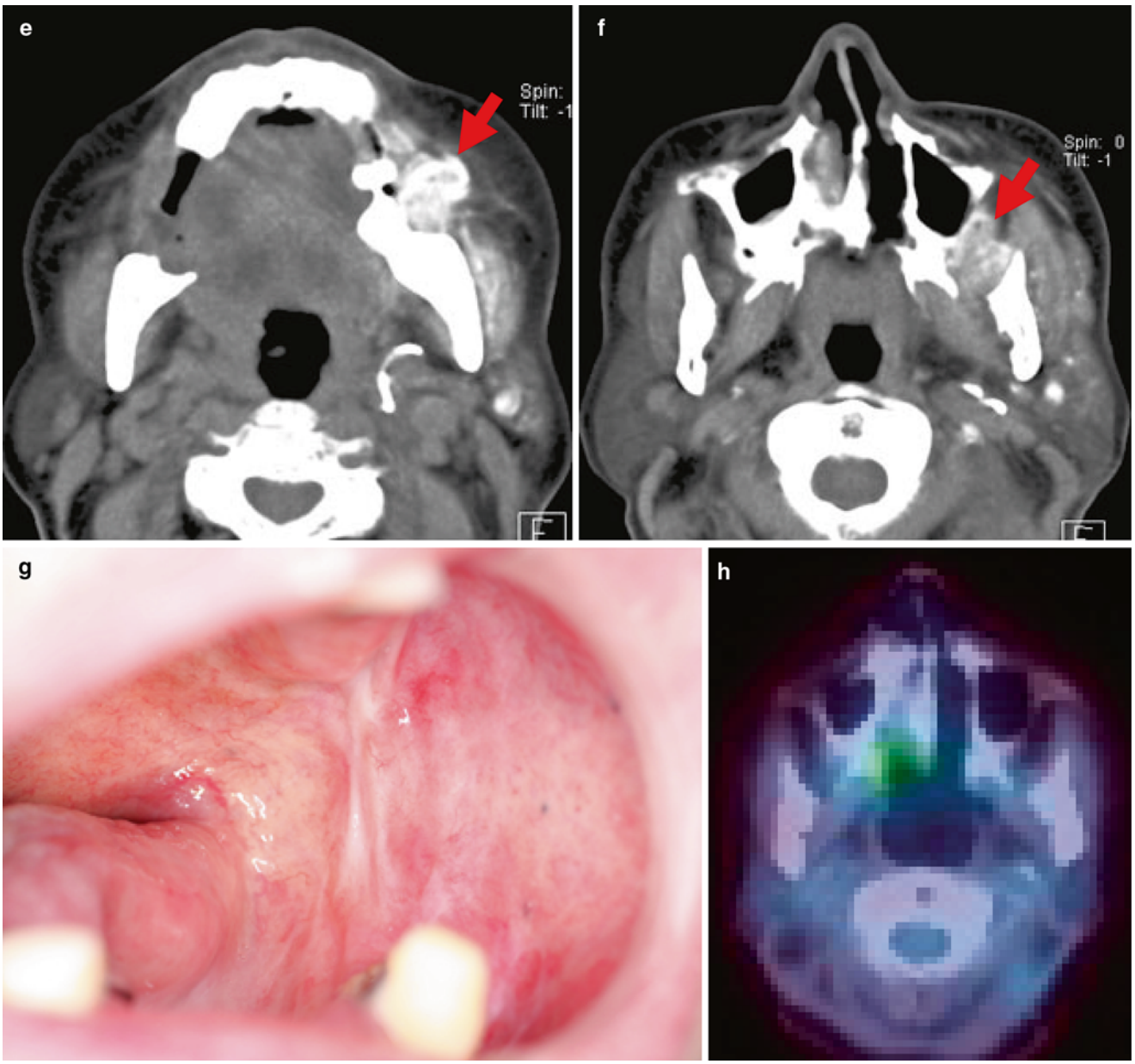

Fig. 13.11 (continued)

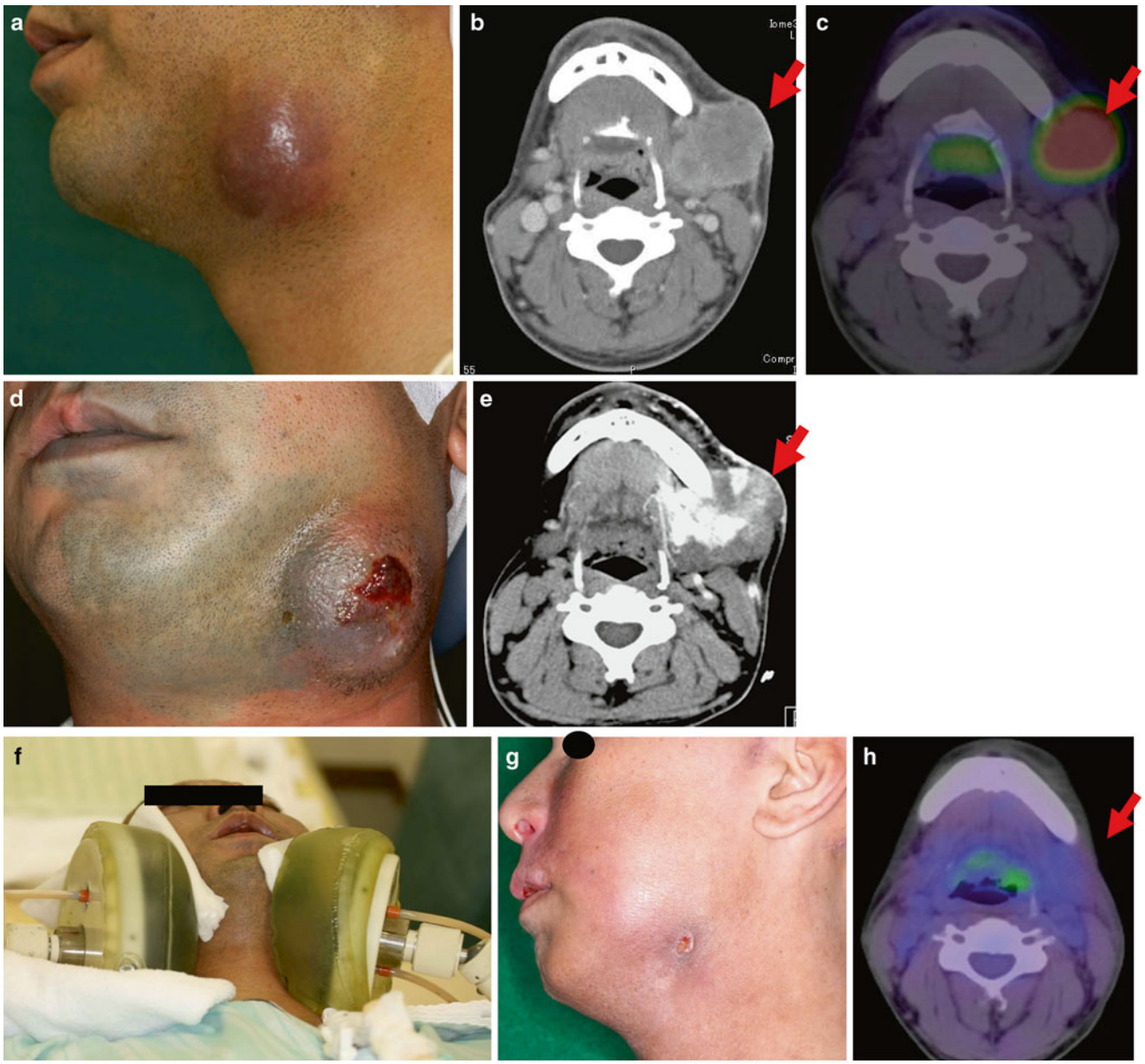

Fig. 13.12 Squamous cell carcinoma of the upper gingiva (T2N3M0). The patient has a large neck mass measured at 85 × 32 mm on the left side of the neck (**a**), and enhanced CT reveals a ring-enhanced mass in the left level II of the neck (**b**, *arrowhead*). PET–CT demonstrates high FDG uptake at the left cervical lymph nodes (SUV max: 13.2) (**c**, *arrowhead*). Two catheters are superselectively inserted into left FA and MA via left STA and OA. Dying of the skin surface of the N3 disease is confirmed by the injection of indigo carmine (**d**), and tumor stain is seen with the use of contrast medium via FA for the N3 cervical lymph node metastases on the flow-check angio-CT (**e**, *arrowhead*). Treatment consists of superselective intra-arterial CRT (DOC total 60 mg/m^2; CDDP total 150 mg/m^2, total 60 Gy) and HT (**f**) for 6 weeks. Five sessions of HT are given for cervical lymph node metastases. HT is administered for 50 min within 30 min after each session of CRT. The temperature of the central and peripheral skin surface of the neck tumor is over 42 °C. After the completion of treatment, N3 disease is much smaller than before treatment (**g**), and pathological complete response has been achieved at the primary site. FDG uptake on PET–CT of the N3 lymph node metastases has disappeared (**h**, *arrowhead*). Radical neck dissection has been carried out, and pathological complete response is recognized in the N3 cervical lymph node metastasis

nized at the N3 cervical lymph node metastasis. The patient has been free of disease for 5 years and 6 months.

13.14 Conclusion

Retrograde superselective intra-arterial infusion has become feasible for daily concurrent radiotherapy and chemotherapy. This combination CRT approach can preserve organs and minimize functional disturbances.

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