Chapter 8
Management of Nodal Metastases

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Introduction

Cutaneous squamous cell carcinoma (CSCC) is the second commonest malignancy in the world, after basal cell carcinoma. Despite this, the number of patients developing metastatic CSCC is relatively low with incidence rates of 2–3 % documented [1], but is increased (10–30 %) in a subset of what is often referred to as 'high-risk' patients [2, 3]. There are well-documented clinic-pathological features defining a high-risk patient and this topic is discussed in depth in other chapters of this book. The aim of this current chapter is to discuss the management of a patient presenting with nodal metastases.

The first site of metastatic CSCC is nearly always to regional lymph nodes within the lymphatic drainage of the primary (or index) CSCC. Patients developing non-nodal metastatic CSCC as a first site of disease are very rare and generally incurable. Consideration should also be given to excluding other primary sources for metastatic SCC such as lung cancer in smokers. Although nodal metastases are also relatively rare in CSCC patients, the absolute number of patients developing nodal metastases from CSCC is not inconsequential. For example, an estimated 5600–12,500 persons develop nodally metastatic CSCC annually in the U.S. [4]. The development of nodal metastases can have catastrophic consequences for the patient with a minority dying of their disease despite treatment. Death is usually a result of uncontrolled regional recurrence (86 %) and to a lesser extent the development of

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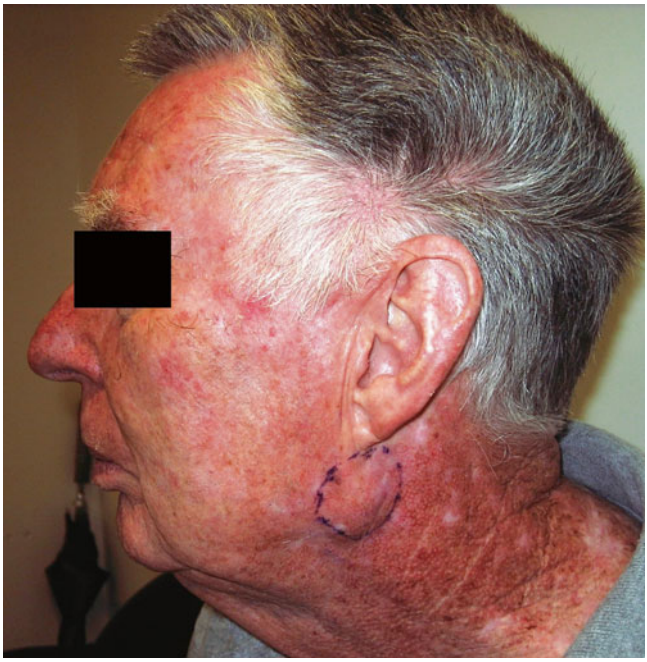

Fig. 8.1 Sixty-three year old male with a 3 cm mobile metastatic lymph node containing CSCC located in his left parotid tail. The patient did not have an identifiable index lesion within the draining ipsilateral head and neck but had previous ablative treatment over the years for superficial actinic lesions

distant metastases (14 %) [5]. Thus any strategies aimed at improving regional control are almost certainly going to positively impact a patient's chance of cure.

The head and neck (HN) is overwhelmingly the site of preference for the development of CSCC nodal metastases, reflecting the higher incidence of primary CSCC in this sun-exposed region. Caucasian males aged >60 years old are typically the most frequently afflicted (Fig. 8.1), although younger men and females also can develop nodal metastases. In most institutional series ~10 to 15 % of patients with metastases are immunosuppressed, either secondary to organ transplantation or haematological malignancy (e.g. chronic lymphocytic leukemia) [2, 5]. Most patients developing metastatic disease do so within a year following treatment of the primary lesion, but can present up to 3–4 years post treatment [6]. Patients may also present with metastatic nodal disease with no known (or suspected) primary site [7], although invariably these patients have a past history of treated skin cancer.

The parotid gland and its associated lymph nodes, is the commonest site for the development of metastatic nodes and has been previously termed "the metastatic basin" for metastatic CSCC [8]. Parotid gland involvement occurs in approximately two thirds of patients with metastatic CSCC of the HN, with the remaining one third developing cervical (levels I–IV) nodal metastases without parotid gland involvement. Because of the visible aspect of enlarging HN nodes most patients will be

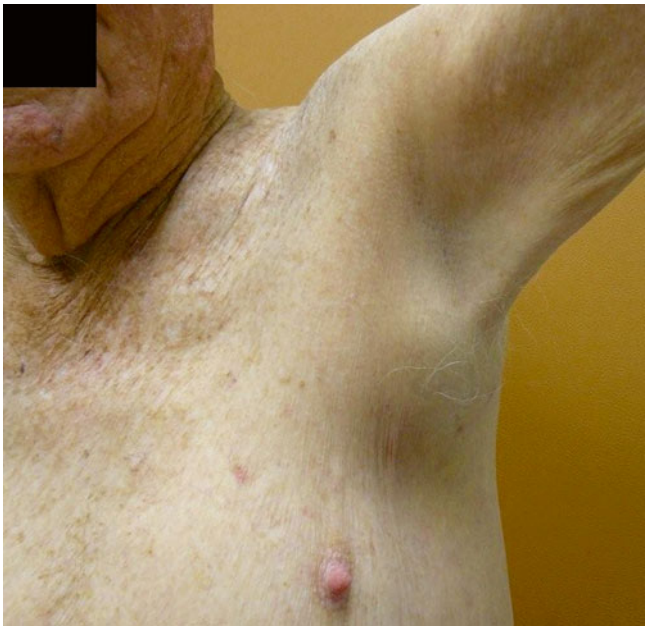

Fig. 8.2 Seventy-five year old male with a large 8 cm mobile metastatic lymph node located in his left inferior axilla. Biopsy confirmed CSCC noting he had previously had a CSCC excised from his left forearm 15 months previously. The patient proceeded to axillary dissection followed by 5 weeks of adjuvant radiotherapy

found at diagnosis to have 1–2 metastatic nodes 20–30 mm in maximum dimension [2]. Metastatic nodes are more often located inferiorly within the parotid tail and clinically may be difficult to distinguish from level II nodes (jugulo-digastric nodes). Less often patients will present with a more superiorly located pre-auricular nodes that may extend superiorly to the level of the zygoma. It should be noted that metastatic nodal SCC involving the parotid almost never arises from a mucosal SCC, excepting in rare retrograde lymphatic spread in patients with already advanced cervical nodal metastases. The axilla and groin are also regional sites for the development of metastatic nodes, often from an extremity or truncal primary (Fig. 8.2).

Patients who develop nodal metastases should be referred and managed within the confines of a multidisciplinary unit experienced in managing patients with this cancer. However, few cancer centers have groups dedicated to managing metastatic CSCC. This plus the rarity of the condition have inhibited development of clinical trials and establishment of clear care standards. Head and neck oncology centers usually have the most experience managing metastatic CSCC but specialist referral for non HN cases is not well-established, even at major cancer centers.

On presentation, patients should undergo a thorough history, examination and relevant investigations often including radiologic imaging prior to any management decision. A history of previous radiotherapy (RT) may impact the ability to deliver

this as an adjuvant treatment. Patients with parotid nodal metastases should have facial nerve function clinically tested to exclude a malignant palsy due to tumor involvement of the facial nerve trunk or one or more of its branches.

Cases occasionally arise of metastatic SCC developing in a cervical node in a patient who is a smoker with a past history of skin cancer but without an obvious mucosal or cutaneous primary. In these patients a positron emission tomography (PET) scan will often aid in detecting a small (<10 mm) mucosal based lesion, with the tonsil and tongue base common sites for detecting an 'unknown' mucosal primary. A nasoendoscopy to visualize the upper aerodigestive tract should also be undertaken. Clinicians ultimately need to decide on the likely origin of the metastatic SCC as the management differs markedly between mucosal and cutaneous primary tumors.

Confirmation of metastatic disease prior to any treatment is mandatory and is usually achieved via a fine needle aspiration biopsy (FNAB). The FNAB should be repeated if the result is equivocal. An open/excisional biopsy is rarely required but may be considered for a small accessible node. High quality contrast enhanced computer assisted tomography (CT) scans of the relevant nodal region are essential and provide valuable information on the extent of macroscopic cancer and its relationship to nearby structures such as the carotid vessels and bones (such as the skull base) (Fig. 8.3). Additional staging investigations could include CT scans of the chest, abdomen and pelvis, although very few patients present with synchronous distant metastases. The addition of other investigations such as magnetic resonance imaging (MRI) scan or a PET scan may be appropriate in select cases but not as

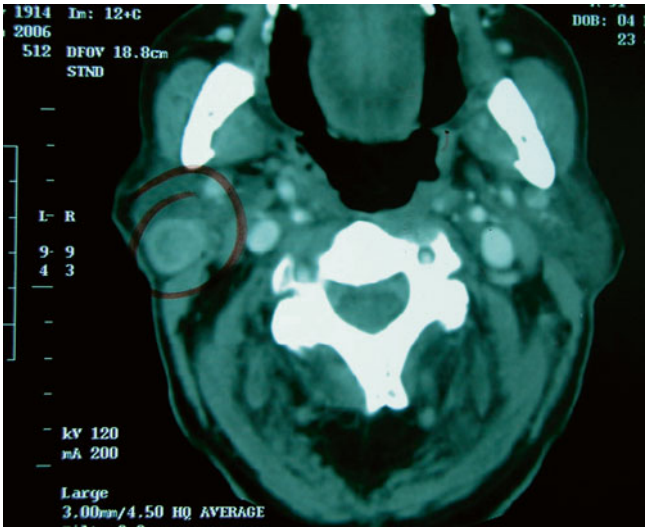

Fig. 8.3 CT scan administered with intravenous contrast highlighting (*black marker pen*) a 2 cm metastatic node located within the posterior aspect of the right inferior parotid gland. Note the contrast enhancement of the circular node with central hypodensity present consistent with necrosis. These are all radiological features typical of a metastatic node containing cutaneous squamous cell carcinoma

routine investigations. A patient's fitness for surgery should also be determined. Medically inoperable patients are often still candidates for high dose RT alone.

The evidence base for recommendations on managing patients with nodal metastases is supported by institutional retrospective/prospective studies [9–11] as there are currently no published randomized control trials comparing treatments. In the majority of patients, the mainstay of treatment is surgery followed by adjuvant RT. Such a combined approach is considered current best practice as supported by published clinical research summarized below. The natural history of relapse in treated patients is dominated by regional relapse in the treated nodal bed, as opposed to distant relapse. It is therefore imperative that appropriate regional treatment is utilized as the best means to cure a patient. Patients that relapse post treatment are rarely candidates for radical salvage treatment and most will succumb to their disease.

There is considerably less published data on CSCC metastasizing to non-HN nodal sites, i.e. the axilla and groin, from CSCC originating on the trunk or extremities. The proportion of non-HN nodal metastatic patients compared to HN metastatic nodal patients is estimated at 1:10 and consistent with the fact that 75–80 % of CSCC are located on the sun exposed HN. While the management of patients with metastatic HN CSCC has become better defined of late, this is not the case with metastatic CSCC to the axilla or groin. It is also unclear if patients with truncal and extremity CSCC have a higher risk of developing nodal metastasis compared with HN CSCC. A German study [12] reported a metastatic rate of 3.9 % for CSCC originating on the trunk and extremities versus 3.3 % for all locations, while an Australian study [13] reported a rate of 4.9 % in 695 patients. Similarly it's unclear if these patients have a worse outcome compared to HN CSCC but limited data would suggest this possibly to be the case. This could be due, in part, to delayed presentation, as unlike in the HN, metastatic disease in the axilla or groin is often difficult to detect until the nodal burden is significant. It may also be that non HN patients are treated with less aggressive surgery and radiation due to concerns regarding lymphedema and thus have a higher risk of relapse.

Role of Surgery in the Head and Neck

Low-Risk Patients

Patients presenting with metastatic nodal CSCC, unless contraindicated, should proceed to an appropriate operation. The majority of these patients will subsequently proceed on to a 6-week course of adjuvant RT to eradicate residual microscopic CSCC. A minority of patients (10–15 %) may avoid adjuvant RT if they are deemed as 'low-risk' for harboring microscopic CSCC and therefore unlikely to benefit markedly from adjuvant RT. In these cases the risk of subsequent regional relapse must be balanced against the acute and potential late side effects of RT and the need for 6 weeks of daily treatment. In a study by Ebrahimi et al., 33 patients with a single involved node <3 cm, with no extracapsular spread (ECS), experienced a 5 year disease specific survival of 97 % when treated with surgery alone

[14]. Such low-risk patients who may avoid radiation must not be immunosuppressed, have undergone elective dissection of the next echelon of lymph nodes and, particularly in the case of parotid metastases, have documented negative excision margins. If all these criteria are met a policy of close observation is feasible but should be discussed with the patient.

Contraindications to Surgery

A minority of patients will present with very advanced nodal metastases that may preclude surgery as an option. Patients with skull base bone invasion and/or carotid artery encroachment may be considered technically inoperable, depending on the clinical situation and surgical opinion and may be offered definitive RT as an alternative. Resecting an involved facial nerve up to the ganglion to achieve a clear resection margin is feasible in select patients treated in skull based units. Such patients nearly always still warrant adjuvant RT [15]. Cutaneous involvement as a result of tumor fungation and associated dermal involvement is not necessarily a contraindication to surgery but will require wide excision or Mohs micrographically controlled clearance of all involved tissues and often large or free-flap reconstruction (Fig. 8.4). Patients with a malignant facial nerve palsy are also still considered operable, assuming no intracranial spread, but will require sacrifice of the facial nerve. These patients should have an MRI pre-operatively to exclude intracranial disease. Patients may also suffer from medical co-morbidity that places them at high risk of perioperative morbidity/mortality, which precludes them from undergoing general anesthesia and surgery (Fig. 8.5). These patients may also be unable to tolerate an extended course of high-dose definitive RT (60–70 Gy) but could still be considered for a shorter course of RT (2–5 weeks). Rarely patients are unsuitable for any RT but if so should be offered best supportive care.

Treatment of the Parotid

In the setting of a functioning facial nerve there is no convincing evidence that outcome is improved by more aggressive surgery in the form of a radical parotidectomy (deep lobe excision and nerve sacrifice), compared to a facial nerve sparing superficial parotidectomy followed by adjuvant RT [16]. Radical parotidectomy is reserved for patients who present pre-operatively with a malignant facial nerve palsy involving multiple branches of the facial nerve or who are found to have facial nerve involvement intra-operatively. In cases where the facial nerve is sacrificed, we recommend that frozen section be performed on the proximal nerve stump to ensure that a clear margin of excision has been obtained. Where possible the divided facial nerve or its branches should be anastomosed primarily or a cable nerve interposition graft utilized. Most patients who undergo nerve grafting have return of facial nerve function within 9 months, but maximal function may take up to 2 years to develop

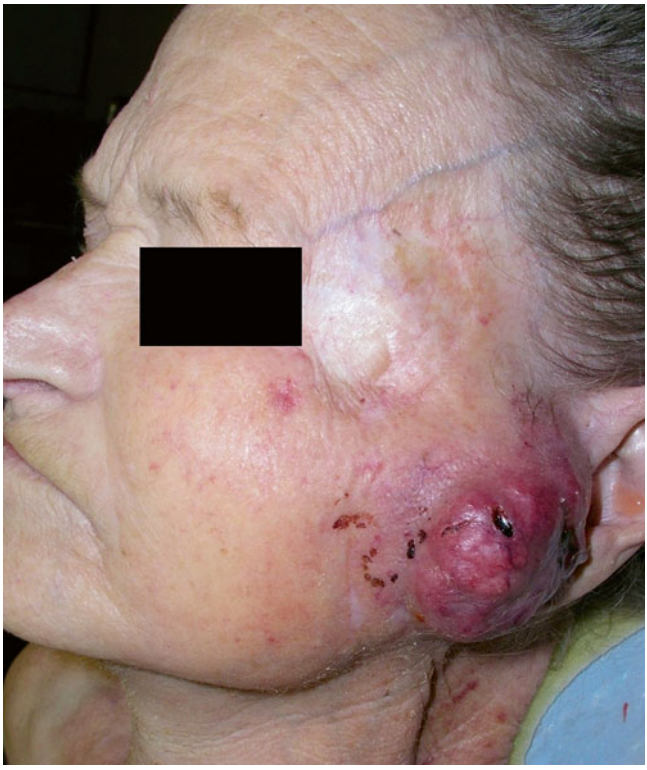

Fig. 8.4 Seventy-nine year old female with a large metastatic lymph node in her left pre-auricular parotid gland. Note the areas of ulceration and surrounding cutaneous erythema indicating dermal infiltration by cancer. The patient had previously undergone excision of a left temple squamous cell carcinoma (note the skin graft). She subsequently required wide excision of the involved tissue, in addition to a parotidectomy and neck dissection, reconstruction with a free flap, and post surgical adjuvant radiotherapy

[17]. Where possible, static re-animation should be performed at the time of grafting/anastomosis in order to provide the patient with immediate form and function before nerve function returns. Despite some concern, the addition of adjuvant RT has been shown not to have a negative impact on facial nerve function following repair [18]. The morbidity of a facial nerve palsy should not be underestimated, even with attempts to graft or re-animate. However interestingly, in at least one study of patients treated for metastatic HN CSCC, facial nerve sacrifice did not appear to adversely impact quality of life [19].

Oncological excision margins (>5 mm) are rarely achieved in patients who undergo nerve-sparing /superficial parotidectomy, especially at the deep plane close to the facial nerve. Studies have documented high rates of close or incomplete excision (40–65 %) following parotidectomy. ECS is also a common pathological finding (30–75 %) and in combination with a close or positive margin adds weight to the importance of adjuvant RT to improve regional control and may explain the high

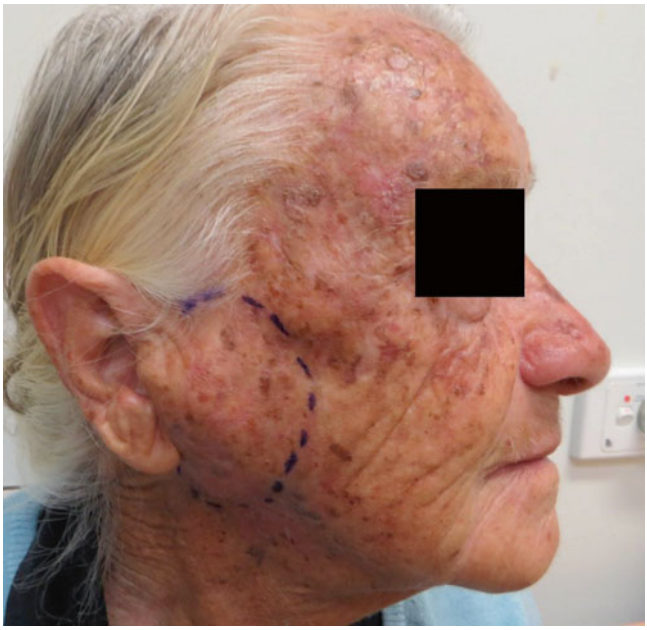

Fig. 8.5 Eighty-eight year old female with a large metastatic lymph node occupying the right parotid gland. Clinically the mass was fixed but the patient's facial nerve was still functioning. Medical co-morbidity precluded her undergoing a total parotidectomy/neck dissection and adjuvant radiotherapy. She was subsequently recommended high palliative radiotherapy utilizing high dose electrons to a total dose of 50 Gy in 20 fractions using a shrinking field technique after 10 fractions and not treating the lower neck. Treatment was well tolerated with a complete clinical response by treatment end

recurrence rate following surgery alone. A study by Iyer et al. demonstrated that in patients who had undergone a nerve-sparing parotidectomy and adjuvant RT, those who had involved margins adjacent to the facial nerve did not have a significant increase in local recurrence and no difference in survival, compared to those with clear margins of excision [16]. We recommend that all these patients undergo adjuvant RT to reduce the risk of regional recurrence.

Neck Dissection

Clinically Node Negative Neck

In patients with parotid metastases and a clinically node negative neck there is a documented incidence of occult cervical nodal metastases in a minority of patients [20] (Table 8.1). We recommend that these patients undergo a parotidectomy and a selective neck dissection (SND) followed by adjuvant RT (if appropriate). The extent of SND will be dictated by site of the primary (or index) lesion: for most

Table 8.1 Surgery according to primary site, parotid involvement, and nodal status

Clinical stage	Primary site	Surgery
P0 N+	Any	CND
P+ N+	Any	Parotidectomy + CND
P+ N0	Anterior/external ear	Parotidectomy + SND (levels I–III)
P+ N0	Posterior scalp/neck	Parotidectomy + SND (levels II–V)

CND comprehensive neck dissection, *N+* clinically evident cervical metastases, *N0* no clinically evident cervical metastases, *P0* no clinically evident parotid metastases, *SND* selective neck dissection

primary sites, a level II–III neck dissection is sufficient, with the addition of level I when the primary is located on the midzone of the face. In the case of a primary located on the posterior scalp or neck, the addition of level IV and V is recommended [21] based on data summarized in the next section.

Clinically Node Positive Neck

Traditionally patients presenting with clinically positive regional metastases in the neck underwent a modified radical neck dissection (MRND) (i.e. resection of levels I–V with preservation of one or more of the following: internal jugular vein, sternocleidomastoid muscle and accessory nerve) rather than a SND. In a study comparing outcome of patients undergoing either a MRND or SND, there was no significant difference reported in 5 year overall survival (61 vs. 57 %; $p=0.86$), noting also that the majority (84 %) of patients also received adjuvant RT [22]. Studies in the setting of mucosal HN SCC also support performing a SND in selected patients in reducing the risk of surgical morbidity compared to a MRND [23].

In a large study of patients undergoing neck dissection for clinically positive neck, involvement of lymph nodes at different levels of the neck were documented and correlated with the site of the primary index CSCC [24]. The authors observed that level I metastases in the absence of level II or level III involvement is observed more commonly in patients with midline facial lesions (Fig. 8.6). In addition, the involvement of levels IV and V was analyzed, which demonstrated that no lesions of the external ear developed nodal metastases to levels IV or V, and only 2.7 % of lesions arising on the face or anterior scalp developed nodal metastasis to levels IV or V. However, the involvement of levels IV and V was higher (15.8 %) in patients who had CSCC located on the posterior scalp and neck. Based on these findings, SND including levels I to III is suggested for patients with primary tumors of midline facial structures, SND including levels II to III for patients with primary tumors of anterior scalp and external ear, and SND including levels II to V for patients with primary tumors of posterior scalp and neck. The external jugular node, which is not assigned to a specific level although often included as a level II node, should be excised in any neck dissection. This node is located superficial to the sternocleidomastoid muscle just inferior to the tail of the parotid adjacent to the external jugular

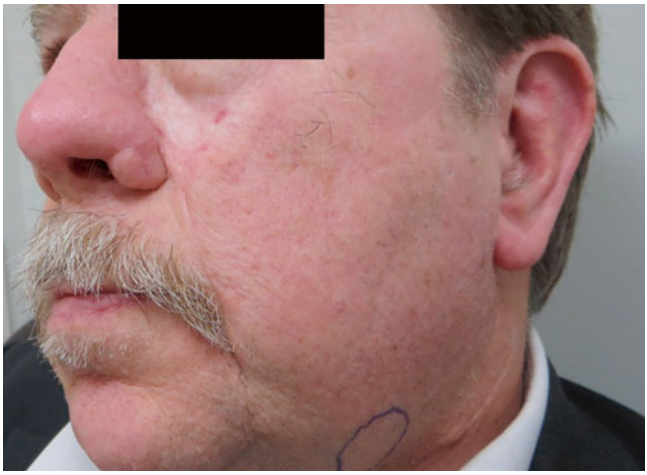

Fig. 8.6 Fifty-six year old male with a 2 cm mobile metastatic node in his left level 1B neck secondary to a previously treated left nasal squamous cell carcinoma (note the local flap and graft reconstructions). The time interval between primary treatment and nodal metastases was 3.5 years. There was no evidence of parotid gland involvement and thus the parotid was not treated

vein. Involvement of this node is pathognomonic for spread from a cutaneous malignancy.

Extended Resections Requiring Reconstruction (Secondary to Skin Involvement)

A minority of patients with HN CSCC nodal metastases present with cutaneous involvement and may require large excisions of skin and subcutaneous tissue as well as parotidectomy and/or neck dissection. When large areas of skin are removed, subsequent treatment must be taken into consideration when planning reconstruction. If the patient is to undergo adjuvant RT, the tissue must be sufficiently robust and the wound healed. Some patients may need reconstruction using a pedicled flap such as pectoralis major flap, or a free flap, particularly if the site has previously been irradiated; radial forearm and latissimus dorsi free flaps are frequently used to reconstruct soft tissue and skin defects in the HN.

Role of Surgery in the Axilla and Groin

The incidence of CSCC metastasis occurring in nodal basins other than the cervical or parotid region is low, with studies reporting rates of ~4 to 5 % [13]. There is a paucity of literature regarding the management and outcome of patients with nodal metastases in these locations. A study of 136 patients with CSCC of the trunk and

extremities developing axillary or groin metastases reported patients having a high risk of recurrence and death [25]. An Australian study of 695 patients with CSCC of the trunk and extremities documented a 4.9 % rate of nodal metastasis, a large number of which were considered inoperable, and with a mortality rate of over 70 % in those developing nodal metastases [13]. Another study of patients with axillary or groin metastases reported a 27 % rate of recurrence following treatment, the majority occurring at distant sites with all patients succumbing following recurrence [26].

Mullen et al. recommended that patients with advanced loco-regional CSCC of the trunk or limbs undergo surgery provided the risk of morbidity and mortality is acceptable [25]. We recommend that patients with operable axillary nodal metastases undergo level I–III axillary lymphadenectomy and those with inguinal disease undergo an inguino-pelvic node dissection, followed by adjuvant RT if indicated. Currently there is no evidence to support the routine use of adjuvant chemotherapy in this setting, with the exception of perianal or anal margin SCC. The etiology of these SCCs is often virally related (Humanpapilloma virus) and the course can be rapidly progressive with a very high risk of metastasis akin to anal carcinoma. Subsequently treatment is along the lines of an anal canal SCC [27].

Of note patients with metastatic CSCC to the inguinal lymph nodes should be assessed for primary SCC of the anogenital region. As with metastases to the HN, a primary or index lesion is not always present or suspected on history.

Role of Adjuvant Radiotherapy

Current evidence supports surgery and adjuvant RT as best practice in operable HN patients with the exception of low-risk patients who may avoid radiation as discussed above. Considering the heterogeneity of patient, tumor and treatment factors across multiple studies, a patient treated with a combined approach overall has a 10–15 % chance of developing regional relapse. The aim of adjuvant (or postoperative) RT is to treat and eradicate residual microscopic CSCC within the operative bed (parotid and/or neck) and also within undissected nearby nodes that may contain (not clinically detectable) occult metastatic CSCC.

Current RT delivers megavoltage energy X-rays (or photons) using machines referred to as linear accelerators. Photons impart lethal double stranded DNA damage to dividing malignant cells as well as normal tissues within an irradiated volume. It is a therapeutic difference in DNA repair between normal and malignant cells that provides the therapeutic ratio of fractionated (i.e. daily) RT. Current technology allows for the conformal delivery of accurately defined RT 3D target volumes that limit many of the toxicities associated with older less conformal, and less accurate, 2D technology.

A typical daily treatment (or fraction of RT) takes 10–15 min to deliver each day Monday to Friday over 6 weeks. Based on analogous data from other tumor sites, adjuvant RT will reduce the relative risk of recurrence by ~50 to 60 % and patients should understand that the aim of adjuvant RT is to reduce, but not eliminate, the risk of relapse.

Recent Evidence

The evidence, albeit institutional and non-randomized and mostly from Australia, supports the addition of adjuvant RT in reducing the risk of regional recurrence and that the majority of patients with nodal disease should be considered for combined treatment. Publications from the Westmead Hospital Group, Sydney, have documented the outcome of a large number of patients treated with a consistent approach since the 1980s, with operable patients undergoing surgery followed by adjuvant RT. The most recent analysis from this group confirmed a significant decrease in regional relapse (23 vs. 55 %) and improved 5 year disease free survival (74 vs. 34 %; $p=0.001$) with the addition of adjuvant RT compared to surgery alone [9]. In a large Australian study Bron et al. reported adjuvant RT as the only factor that significantly improved control in the parotid and recommended it as standard treatment [28]. Similarly, Del Charco et al. documented treatment (surgery/RT vs. RT) as the only factor to predict parotid disease control on multivariate analysis ($p=0.004$) [29] and Jol et al. reported decreased locoregional failure in patients undergoing surgery and adjuvant RT compared with surgery alone (17 vs. 44 %) [30].

In at least one Australian study the finding of soft tissue metastases (STM), defined as free soft tissue deposits lacking continuity with the primary tumor and not associated with nodal tissue, portended to a worse prognosis. After adjusting for other covariates STM was an independent predictor of worse survival. The authors suggested patients with STM be considered for combined treatment, irrespective of other factors. Further studies are still needed to confirm this association but similar to the finding of ECS it would be prudent to recommend adjuvant RT in STM patients also [31].

Elective Treatment

The role of elective treatment, be that RT or surgery, to uninvolved cervical nodes is controversial. Two Australian studies have documented a 35 % rate of subclinical metastases in dissected clinically negative neck nodes in patients with metastatic parotid nodes following elective neck dissection [10, 20]. This compares with a lower incidence (16 %) of occult spread in neck nodes in a Canadian study by Audet et al. [32] while a study from the MD Anderson Cancer Centre, Texas documented a higher 42 % incidence of occult cervical metastases in patients with metastatic parotid SCC [33]. Despite variation these and other studies suggest that a minority of patients will harbor subclinical nodal metastases that left untreated will progress to clinically enlarged nodes in many patients. The risk is therefore of clinical progression and the associated morbidity and mortality as the size and number of metastatic nodes increases. Identifying individual patients at greatest risk is difficult and although close observation may be an option, patients need to be reviewed regularly (every 3–4 months) for 4–5 years.

An accepted practice for patients with parotid metastases, and a clinically negative neck, is to undergo a SND (levels I/II or I/II/III) in conjunction with a parotidectomy. Deleting a neck dissection in the setting of parotid metastases and a clinically N0 neck is an option. However this will commit all patients to receive elective RT (50 Gy) to the hemi-neck. Although it is well accepted that neck control is equivalent in a clinically N0 neck with either surgery or RT the finding of pathologically negative upper level neck nodes may result in a patient avoiding adjuvant RT to the lower neck. Patients with clinically positive cervical nodes should undergo an appropriate neck dissection. Adjuvant RT is delivered to the ipsilateral neck if cancer is identified in multiple nodes ($\geq$2) or extranodal spread is present in a single node.

A scenario occasionally encountered is that of a patient with an index lesion located on the temple/forehead or ear with nodal metastases in the cervical nodes, but without nodes involving the parotid gland. The mechanism of this 'skip' spread is unclear. The question arises in these cases of whether elective treatment to the intervening parotid nodes is warranted. There is no data to guide clinicians but patients undergoing adjuvant RT to the dissected neck may benefit from the extension of fields to also encompass, at a minimum the lower parotid nodes (i.e. tail of parotid). An alternative would be to perform a nerve sparing parotidectomy in conjunction with the neck dissection and thereby potentially avoid the added toxicity of RT to the oropharynx/oral cavity from the exiting RT beams.

Similarly, some clinicians may consider electively treating a presumed index lesion if the development of metastatic nodal CSCC has arisen within a relatively short defined interval from initial treatment to the development of metastatic nodes (e.g. <12 months) and unfavorable features were present such as a close or positive margin. There is however no evidence to support this approach and in the setting of a controlled primary lesion we would not recommend electively treating the primary site with either surgery or RT.

Technical Aspects of Radiotherapy (Dose Fractionation Schedules/Volumes to Treat)

Adjuvant RT is usually delivered to the ipsilateral neck and/or parotid gland and rarely, if ever, requires a comprehensive (i.e. bilateral) approach. The toxicity of RT, while not inconsequential, does not involve the treatment of large areas of mucosa, compared with mucosal based primary HN SCCs (e.g. tongue base SCC). The predominant acute toxicities of comprehensive mucosal HN SCC are painful mucositis (odynophagia) and xerostomia which are not a major concern with ipsilateral parotid RT. The expected acute toxicity of ipsilateral RT that encompasses the parotid bed includes mild xerostomia, alteration in taste, skin erythema/desquamation and fatigue. The addition of hemi-neck RT to the superior parotid fields will add to the extent of skin treated and possibly the degree of fatigue experienced. Late

toxicities include potential hearing impairment if the superior extent of the treatment volume includes the middle ear structures and also a degree of ongoing xerostomia. Patients with poor dentition would benefit from pre-RT dental assessment that may result in extraction of posterior lower molar teeth that may be in the treatment field.

A dose fractionation schedule of 60 Gy in 30 daily fractions is recommended as best practice to post-operative (at risk) volumes. Clinicians may elect to boost smaller volumes with positive margins to 66–70 Gy (from 60 Gy). Undissected necks (or parotid) can be prescribed 50 Gy in 25 fractions when receiving elective treatment. Alternative dose fractionation schedules utilizing 2.5–3 Gy fractions may be considered in select patients to reduce the duration of treatment but most should receive 2 Gy fractions to minimize potential late toxicity. The use of altered fractionation in the adjuvant setting, as a means to improve locoregional control, is not standard but has been reported. The University of Florida Group have used hyperfractionation (74.4 Gy in 1.2 Gy twice daily fractions or similar) for many years in select patients with advanced and metastatic skin cancers and reported good results [34].

The delivery of adjuvant RT should optimally be commenced within 6 weeks of surgery. All patients should be treated with contrast enhanced (if not contraindicated) CT planned conformal RT to accurately define planning target volumes and important organs at risk (e.g. eyes, brainstem, middle ear and spinal cord). The use of highly conformal intensity modulated RT (IMRT), if available, may be considered, especially in cases where perineural invasion (PNI) involving the trunk, or branches of, the facial nerve, as this warrants the consideration of extending RT coverage beyond the skull base to encompass the intracranial extent of the facial nerve, in some cases back to the brainstem. In these circumstances an IMRT approach may provide better coverage and less toxicity to central nervous system structures [35].

The addition of bolus (tissue compensation) to either surgical scars or the irradiated skin of the parotid and/or neck with the aim to increase the dose delivered to the skin is not recommended unless there is known cutaneous involvement. Even in these circumstances the increased skin toxicity (in-field moist desquamation) may result in some circumstances in the requirement of a RT treatment break to allow for healing with at least one Australian study documenting increased cutaneous toxicity and no outcome benefit from this approach [36].

Role of Adjuvant RT in Non-HN Regions

Analogous to recommending adjuvant RT to the parotid and/or neck is treating the axilla or groin after nodal surgery. Although less published data is available to guide the clinician in assessing risk of recurrence associated with unfavorable factors such as ECS, patients with multiple involved nodes or close excision margins are at risk of developing regional relapse and should be recommended adjuvant RT. The aim of RT is to decrease this risk, in keeping with data from the HN setting. A complication of axilla or groin adjuvant RT, in contrast to the HN, is the risk of the development of extremity lymphedema, which is exacerbated post surgery by the addition

of adjuvant RT and in a minority of patients, can be severe. Patients need to be warned of this potential late side effect and we recommend that all patients who undergo an axillary or inguino-pelvic node dissection and/or radiotherapy be referred for lymphedema education and management.

Axillary RT is easily achieved using CT 3D conformal planned opposing AP/PA megavoltage photons and attempting to minimize the amount of underlying lung irradiated, taking into consideration the curvature of the chest wall and the need to cover the often medially located axillary nodes. The supraclavicular fossa should also be included in the treatment fields. This technique is well defined using anatomical landmarks with one study reporting excellent regional control rates and minimal late toxicity [37]. The risk of brachial plexus plexopathy and rib fractures can be minimized by limiting the total dose delivered to 50 Gy in 25 fractions. Other authors have treated to a higher dose of 60 Gy equivalent to the dose recommended in HN regions [38].

The groin is also usually approached with either opposing AP/PA megavoltage photon fields or with a high energy electron field. Various techniques are reported, often depending on whether the hemi-pelvis (to treat deeper pelvic nodes), as well as the groin, are to be treated. With involved nodes often in close proximity to the underlying femoral head, groin RT carries with it a risk (10–15 %) of late femoral neck fracture. Despite this, inadequate deep coverage (5–6 cm) in an attempt to decrease the dose to the femoral head, especially using electrons, may undertreat deeply located nodes and increase the risk of regional relapse [39].

Inoperable Metastases

Radiotherapy Alone

Patients with skull base bone invasion, brain or carotid vessel involvement should be considered inoperable, but still treatable. Such patients usually present with very advanced disease, which is frequently fixed to underlying structures. In the case of metastatic CSCC occurring in nodal basins other than the HN, it is less common to encounter a patient who has unresectable disease. More frequently, the patient is not a candidate for surgery due to co-morbidities.

In patients with operable nodal disease that are treated with high dose (66–70 Gy) RT (medically unfit/patient refusal of surgery) there is a chance of cure although patients with more advanced borderline operable or inoperable disease are unlikely to obtain durable regional control.

Palliative Radiotherapy

Patients who are unsuitable for surgery and/or 5–6 weeks of RT due to poor performance status may still benefit from shorter schedules of palliative RT. Examples of recommended dose fractionation schedules include 20–25 Gy in 5 fractions, 30–35 Gy in 10 fractions or 40–45 Gy in 15 fractions (Fig. 8.7). Clinicians should

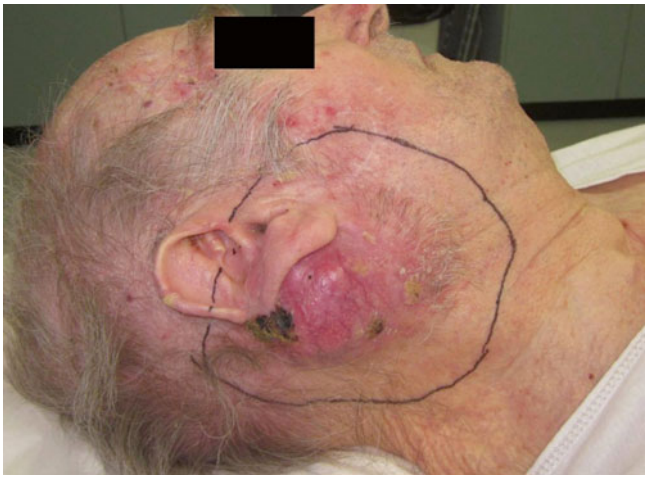

Fig. 8.7 Elderly nursing home patient of poor performance status with an advanced metastatic tail of parotid node treated palliatively with a moderate energy (12 MeV) electron field (as marked) to a dose of 25 Gy in 5 daily fractions to obtain growth restraint and tumor reduction and prevent fungation

consider limiting irradiated volumes to macroscopic disease with 1–2 cm margins using simple techniques such as opposed megavoltage photons fields or a direct electron field. In a Canadian study [40] patients with advanced HN CSCC (median size 5 cm) not suitable for radical treatment received 24 Gy of RT in 3 divided fractions delivered on days 0, 7 and 21 over 3 weeks. A variety of modalities and techniques were utilized and field margins encompassing macroscopic disease were 1–2 cm. The authors reported a complete clinical response rate of 36 % and the alleviation of symptoms in most patients without any marked late toxicity. The choice of which palliative dose fractionation schedule to utilize is dependent on multiple factors but very much dependent on the patient's ability to tolerate prescribed treatment.

Depending on the initial response to palliative RT and the dose delivered, suitable patients may be candidates for further RT to sites of symptomatic disease.

Patients with symptomatic sites of metastases such as skeletal metastases or soft tissue deposits may benefit from a single 6–8 Gy fraction of RT or multiple fractions such as 20 Gy in 5 fractions. Symptoms of pain or bleeding are usually well palliated with local RT. Sites of painful nodal metastases are better treated with a fractionated approach as opposed to a single fraction.

Role of Chemotherapy

Adjuvant Radio-Chemotherapy

Chemotherapy is also discussed in Chap. 9, particularly with regard to palliative therapy in terminal cases. Combined chemoradiation for control of nodal disease is discussed below. Despite the current optimal treatment of nodal disease with surgery

and adjuvant RT a minority of patients develop recurrence, predominantly regional in the treated nodal bed. There are data in mucosal HN SCC that combination concurrent platinum chemotherapy and adjuvant RT can improve regional control and disease free survival postoperatively in high-risk patients (ECS, multiple nodes, positive margins) [41, 42]. Though such studies have not been conducted in CSCC, high-risk pathological features such as multiple nodes, extranodal spread, positive margins, and perineural or vascular invasion, are often present in metastatic HN CSCC patients. The first trial testing chemoradiation in such CSCC patients has recently been conducted in Australia and New Zealand under the auspices of the Trans Tasman Radiation Oncology Group (TROG) with the aim to accrue 265 patients randomized to receive adjuvant RT (60 Gy) or adjuvant RT and weekly carboplatin (Post-Operative Skin Trial; POST 05.01). Carboplatin was chosen on the basis that the patients in this study are unlikely to tolerate cisplatin (renal and ototoxicity) as many are older with pre-existing co-morbidities. As of 2014 the study has closed to accrual and analysis and publication of the results is likely in the near future.

Palliative Chemotherapy

Patients with disseminated disease who are of good performance status may be considered for single or combination palliative chemotherapy. As in patients with mucosal HN SCC the combination of 5FU and platinum has been utilized. This is covered more fully in Chap. 9.

Recurrent Disease Post Treatment

Recurrent nodal metastases in a treated nodal bed are associated with a poor prognosis and often associated with subsequent distant relapse despite successful regional salvage. Prior to recommending radical intent salvage treatment, patients should be appropriately re-staged to exclude the presence of visceral (e.g. lung, liver) metastases. Investigations should include whole body contrast enhanced CT scans, or alternatively a CT/PET scan.

Salvage Surgery

Regional SCC recurrence after a previous dissection and/or RT should be re-operated on where possible. The extent of previous surgery and RT and the site of recurrence will dictate the type and extent of salvage surgery. Generally we would recommend patients have a completion neck dissection. Recurrent SCC in the parotid bed following nerve sparing parotidectomy may require salvage radical parotidectomy with sacrifice of the facial nerve. Surgery is often technically challenging, particularly if the patient has had RT previously, as this increases tissue fibrosis and may delay

wound healing. Recurrences often involve the overlying skin, which should also be re-excised with clear margins whenever possible. Pre-operative peripheral margin Mohs micrographic surgery can sometimes be helpful in such cases to establish the lateral extent of skin and subcutaneous recurrence. This helps surgeons to plan reconstruction pre-operatively (since they know in advance how much skin will be lost) and allows them to focus on clearing the deep margin intraoperatively as peripheral margins have already been determined. Adjuvant RT should be offered to all patients who have not previously been irradiated, and should encompass the surgical bed and uninvolved next echelon nodes. Patients considered not suitable for salvage surgery, or that decline surgery, should be offered definitive RT. Doses of 60–70 Gy using CT planned megavoltage photons offer the patient a chance of cure, or at the very least durable in-field regional control. Patients not suitable for high-dose RT should still be considered for a shorter course of RT.

Regional Re-Irradiation

Regional recurrence after adjuvant RT poses a difficult problem as patients will usually have had a large volume (e.g. ipsilateral parotid bed +/-hemi-neck, groin, axilla) of normal tissue (e.g. mandible, soft tissue, brainstem/spinal cord, nerves, carotid artery, femoral head, ribs) irradiated to 50–60 Gy. Following appropriate re-staging, operable patients should proceed to surgery. For inoperable patients the evidence available for re-irradiation relates predominantly to treating mucosal HN SCC patients. In this analogous setting recent evidence has emerged supporting the use of highly conformal IMRT [43, 44]. Patients retreated with IMRT are likely to have a better outcome (improved regional control and decreased severe late effects) compared with conventional 3D conformal re-irradiation. The best results are achieved with radical re-irradiation doses of ~60 to 70 Gy in 2 Gy daily fractions and re-treatment volumes limited to ~2 cm around gross disease or the resection bed. The spine, brainstem and optic chiasm should receive a limited re-treatment dose (15–25 Gy) if previously irradiated to tolerance. Of note, even when utilizing IMRT, serious late toxicity and treatment related deaths are reported in around 20 % of patients. The addition of concurrent chemotherapy to re-irradiation has also been recommended in select patients with mucosal SCC. The role of re-irradiating after salvage nodal surgery is less well defined but in patients with unfavorable pathology (i.e. close/positive excision margins, ECS) it should be considered.

Prognosis

The older literature often reported a dismal outcome for patients developing metastatic nodal CSCC with only a minority curable. However this should not be considered the case with contemporary treatment. The prognosis of patients with metastatic

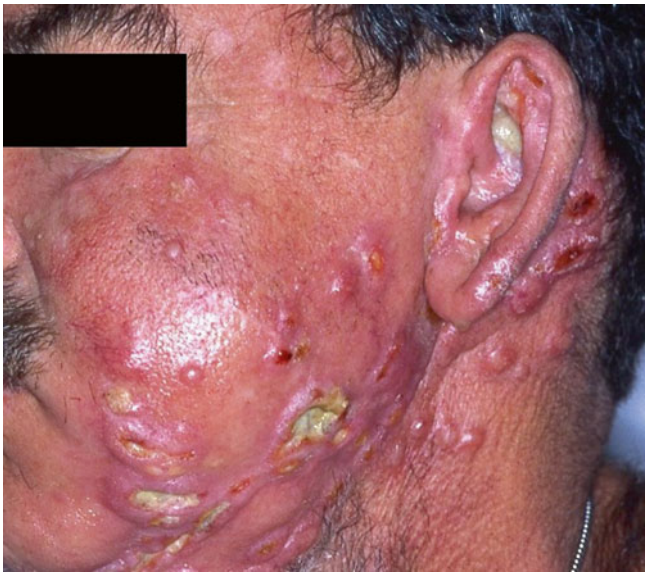

Fig. 8.8 Fifty-two year old male cardiac transplant recipient with widespread dermal based metastases following recent surgery and adjuvant radiotherapy with metastatic cutaneous squamous cell carcinoma to the left parotid. The patient was incurable and after cessation of his immunosuppressive medications was treated palliatively

HN CSCC if treated appropriately is favorable with most cured with the expectation of a 60–75 % 5 year disease free survival [2, 6, 7]. A large study of 250 patients identified 4 independent predictors of prognosis: immunosuppression, type of treatment, extracapsular spread and surgical margin status (ITEM), and subdivided the patients into three risk categories according them an ITEM score with the 5 year risk of dying from disease for patients reported to be 52 %, 24 % and 6 % for high-risk, moderate risk and low risk groups, respectively [41]. Patients who underwent surgery and adjuvant RT had a significantly improved outcome (hazard ratio 0.32, 95 % CI 0.16–0.66; $p=0.002$) compared with surgery alone, and patients with ECS and/or immunosuppression, fared worse [45]. It is well documented that immunosuppressed patients do badly despite appropriate treatment [46] (Fig. 8.8). Thus the level of immunosuppression should be reduced if at all possible [47].

There has been much less published data regarding the outcome of patients with nodal metastases in areas other than the HN, with some series reporting relapse rates of 30–60 % [25, 37], many with distant sites of first relapse. However most series are small and heterogeneous and it is therefore difficult to make definitive comparisons with metastatic HN CSCC.

New Advances/Studies/Follow up Post Treatment

Until recently, adjuvant systemic treatment for nodal metastatic CSCC consisted of traditional chemotherapeutic agents such as cisplatin and carboplatin. There is ongoing research investigating the use of more novel agents including molecular targeted therapies.

Agents such as interferon α, and 13 *cis*-retinoic acid have shown some activity against CSCC. However, a phase III study of the use of retinoic acid and interferon in the adjuvant setting for patients with "aggressive CSCC" including those with nodal metastases showed this treatment did not improve the time to tumor recurrence or prevent second primary tumors [48]. Epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase which is expressed in CSCC and often over-expressed in metastatic disease. Recently there has been interest in using agents such as cetuximab, an anti-EGFR monoclonal antibody for the treatment of CSCC. A phase II study of the use of cetuximab in patients with unresectable CSCC demonstrated a 69 % response rate [49]. Cetuximab is a known radiosensitizer and several case reports/series have documented its use in combination with RT. In one study of eight patients with either advanced or unresectable CSCC treated with Cetuximab +/-RT the authors reported 6/8 responding with 3 complete responses and a median overall survival of 22.5 months [50]. However, its use in the adjuvant setting for the treatment of nodal metastases of CSCC has not yet been established and remains investigational in this setting.

Abbreviations

CSCC	Cutaneous squamous cell carcinoma
CT	Computer assisted tomography
DNA	Deoxyribonucleic acid
ECS	Extracapsular spread
EGFR	Epidermal growth factor receptor
FNAB	Fine needle aspiration biopsy
HN	Head and neck
IMRT	Intensity modulated radiotherapy
MRND	Modified radical neck dissection
MRI	Magnetic resonance imaging
PET	Positron emission tomography
RT	Radiotherapy
SCC	Squamous cell carcinoma
SND	Selective neck dissection
STM	Soft tissue metastasis

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