Asian Journal of Surgery
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Unknown Primary Squamous Cell Carcinoma of the Head and Neck: A Review of Diagnosis, Treatment and Outcomes

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Introduction

Conventional teaching holds that an adult presenting with a lateral neck lump has cancer until proven otherwise. In fact, as many as 80% of such lesions are malignancies, with the majority being metastatic deposits from a mucosal squamous cell carcinoma. The incidence and patterns of metastatic disease in the neck vary with the anatomical site and T stage of the primary tumour. While most cervical metastases are easily paired with a squamous cell carcinoma of the upper aerodigestive tract, in 5% to 10% of patients, no such primary tumour is immediately apparent. If, after directed imaging and endoscopy, the primary cancer is still not found, the patient is said to have an unknown, or occult primary. This situation poses a significant challenge to the treating clinician with regard to subsequent work-up and treatment options. In the following paper, the management of the occult primary is discussed, along with a description of our institutional experience.

Presentation of the Unknown Primary

Patients presenting with metastatic squamous cell carcinoma from an unknown primary show a male to female preponderance of approximately 3:1 with an average age between 60 and 70 years.[1–9] Tobacco and alcohol are thought to be individual and synergistic risk factors, with an approximate 10 to 15-fold relative risk in persons using significant amounts of each.[10]

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Date of acceptance: 28th December 2001

Typically, the cervical mass is painless, although pain or compressive symptoms in adjacent structures may occur.[6,8] The delay in definitive diagnosis is usually several months, as initial treatment with antibiotics often precedes diagnosis.[11] Metastatic nodes related to occult primaries are most often unilateral, with bilateral disease occurring in approximately 10% of patients.[1,3,5,7,9,12] The most common location for metastatic disease is level II (30%–50%), with levels I and III less commonly involved (10%–20%) and levels IV and V rarely affected (5%–10%).[1,3,7,12] Clinical and radiological evaluation frequently identifies multiple involved nodes, although in 10%–20% of patients, only a single node will be present.[1,3–9,12–14]

Clinical Evaluation

As most lateral neck masses in the adult are malignancies, the clinical history should focus particular attention on previously treated tumours and the likely sites of an unrecognized primary cancer. The level of metastatic involvement may give some clue as to the likely primary site. A submandibular mass (level I) would most commonly be related to a primary in the oral cavity or skin. Level II nodes, including the jugulodigastric node, may point to a primary in the oral cavity, oropharynx, or supraglottic larynx. Middle and lower jugular nodes (levels III and IV) are more likely related to a laryngeal or hypopharyngeal cancer. Tumours of the nasopharynx generally spread to level II or the posterior triangle, as well as retropharyngeal nodes. Skin cancers are common among fair-skinned elderly males and should always be considered during history and physical examination. Metastatic cutaneous malignancy may involve nodes in the parotid tail, the pre-auricular region, level I, or the posterior triangle. An often overlooked node frequently affected by skin cancers is the external jugular node, lying along the anterior border of the upper one-third of the sternocleidomastoid muscle. Metastatic disease restricted

to the supraclavicular region is often due to an infraclavicular primary site.

All patients with a neck mass should undergo a complete head and neck examination, which has been greatly facilitated by the introduction of the flexible nasopharyngoscope. Sites of particular importance are the nasopharynx, tonsil, base of tongue and pyriform sinuses, as these sites may harbour small occult primaries. Palpation, especially for the base of tongue and tonsils, is important, as these sites are often difficult to examine even with appropriate equipment. The hypopharynx is invariably difficult to examine outside the operating room, but pooling of secretions may suggest a neoplasm in this region. Lastly, a survey of the scalp and skin of the head and neck should be routinely performed.

Fine Needle Aspiration Biopsy

Fine needle aspiration biopsy (FNAB) is well established as the method of choice for tissue diagnosis in the evaluation of a neck mass. Large series have shown that, when done correctly, better than 95% of FNAB samples will be adequate for diagnosis, with a 96% diagnostic accuracy rate in the setting of squamous cell carcinoma.[15] Additionally, the morbidity of FNAB is extremely low with minimal contamination of surrounding tissues. Open biopsy, on the other hand, requires an operation, with its attendant morbidity. Additionally, it was previously thought that an open biopsy might adversely affect prognosis, as well as increase wound complications.[16] Several series have since suggested that this is not the case, with no difference between open biopsy patients and matched controls regarding survival, neck control, distant metastases, or wound complications.[17,18] Given its convenience and accuracy, FNAB is preferred, with open biopsy reserved for non-diagnostic FNABs or those cases suspicious for lymphoma.

Imaging

The choice and timing of imaging modalities vary among institutions. Ideally, imaging studies should be performed prior to any invasive procedure or treatment in order to avoid artefact that might accompany these interventions. For instance, biopsy of mucosal sites, and certainly an open biopsy of a lymph node, might cause local oedema or haematoma, making interpretation of subsequent imaging studies difficult. FNAB causes minimal distortion of local anatomy and can be performed prior to imaging.

At most treatment centres, including our institution, computed tomography (CT) scan is the imaging study of choice. It is relatively inexpensive, readily available, and yields excellent anatomical information. In almost all of the reviewed series, CT was used preferentially, although many of these series predated magnetic resonance imaging (MRI).[1,2,5–8,13,14,19,20] The scan should always be with intravenous contrast, and most workers advocate that it should include the region from skull base to clavicles. Some authors recommended inclusion of the chest, especially with low jugular or supraclavicular nodes.[6]

MRI provides soft-tissue definition generally superior to that of the CT and is further enhanced with the use of fat suppression techniques in T2 and postcontrast T1 images.[21] These soft-tissue capabilities make MRI especially useful for examination of the nasopharynx and oropharynx.[22] In fact, because these are common sites for an occult primary, some advocate MRI as a first-line study in that setting, with small case series showing a better sensitivity than CT.[23]

Positron emission tomography (PET), a recently developed imaging modality, also shows promise for the detection of occult primary cancers. Anatomical definition is poor, as for all nuclear medicine studies, but sensitivity is fairly high.[24] Hanasono et al reported a series in which PET correctly identified 35% of primary tumours in patients with a previously unknown primary, as compared to a detection rate of 36% for MRI and 22% for CT scan.[25] When a PET scan was combined with either a CT or MRI, the detection rate increased to 40%.

Examination Under Anaesthesia

If history, physical examination and imaging have failed to detect a primary tumour in a patient with metastatic neck disease, the clinician should proceed with examination under an aesthesia, including detailed endoscopy. If the primary lesion is still not identified, directed biopsies of likely mucosal primary sites should be taken. Most authors advocate so-called 'blind biopsies' in this setting, although opinions differ on which sites should be biopsied. It has been recommended that nasopharynx, tongue base, tonsil and pyriform sinus should all be biopsied ipsilateral to the affected node in every case.[5–9,14] Others recommend that biopsies should be based on patterns of lymph node spread,[3,13] or think

that only macroscopically abnormal mucosa should be biopsied.[2] A mixed approach may also be reasonable, with routine biopsies of the nasopharynx and tonsil, and biopsies of pyriform sinus or tongue base only when the mucosa appears abnormal.[4,12] No study, to date, has examined which strategy has the highest yield, but the issue of tonsil biopsy has been examined. Several authors have reported that only a complete tonsillectomy will adequately sample the tonsil for malignancy, as small tumours, on gross inspection, can go unnoticed in the tonsillar crypts.[26,27] At our institution, we routinely biopsy the nasopharynx and usually perform a tonsillectomy ipsilateral to the affected node. The tongue base and pyriform sinus are biopsied only if a mucosal abnormality is seen. It should be noted that, in our series of unknown primary tumours, of the five patients who subsequently manifested a primary cancer, none had biopsies of those sites performed at initial endoscopy.[1]

Mention should also be made of new technologies employing DNA probes and other genetic markers for the identification of tumours. These methods allow for early detection of malignant change on a molecular level prior to any histopathological sign of cancer. Preliminary studies have shown these techniques to be useful for the identification of unknown primary tumours.[28,29]

Treatment

Surgery

Neck dissection is the standard initial treatment in the setting of an unknown primary,[1,2,4,12] the aim being to encompass the clinically evident disease along with other nodes at risk. A radical neck dissection removes nodal tissues from levels I–V and sacrifices the spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle. A modified radical neck dissection spares one or more of these structures but removes the same nodal tissue. As there is no evidence that radical neck dissection, is superior to modified radical neck dissection every attempt should be made to preserve the spinal accessory nerve, in order to reduce shoulder morbidity. While a 'comprehensive' neck dissection is probably the safest oncological procedure, a role for selective neck dissection, targeting specific nodal groups, is recognized. Patients with clinical disease at levels IV or V could safely be treated omitting level I. Similarly, if nodal disease is limited to level I or II, a selective dissection encompassing levels I through IV, but omitting level V, may be acceptable. Though several series have included patients treated with selective neck dissections, none has looked specifically at outcome as a function of the extent of neck dissection.[1–3] Therefore, there are no data to suggest that a selective dissection, in combination with radiotherapy, is any more or less effective than a comprehensive dissection in the case of an unknown primary.

Radiation therapy – the ipsilateral neck

Radiation therapy is usually prescribed as adjunctive treatment following the appropriate neck dissection. Most would advocate a full course of radiation to the affected neck if more than one node is involved or if extracapsular spread or positive margins are present.[1-3,12,30,31] For pathologically proven N1 disease, radiation to the neck is probably not warranted. Definitive neck irradiation, reserving neck dissection for those with an incomplete response, has also been described.[5–7,14] This approach may be equivalent to surgery with the clinically N1 neck, but most authors agree that combined modality treatment is needed with clinical N2 disease or greater.[1–3,12,30–32] It should also be pointed out that as many as one third of patients with clinical N1 disease are found to have multiple positive nodes when staged with a neck dissection.[2] This has obvious therapeutic and prognostic implications when considering radiation as sole therapy for patients with clinically early disease. With regard to the timing of neck irradiation, postoperative radiation therapy is generally preferred if combined modality treatment is planned, as this reduces the risk of wound complications which may be associated with preoperative radiation. For patients with massive neck disease, preoperative radiation may be used to decrease the dimensions of nodal disease, making the subsequent neck dissection less difficult.

Radiation therapy – the contralateral neck

When both sides of the neck are clinically positive, bilateral neck dissections should be carried out, followed by bilateral radiation therapy. There is debate with regard to the clinically negative contralateral neck. Reddy and Marks showed that control of disease in the clinically negative contralateral neck was 84% when both necks were irradiated, compared to 45% when only the ipsilateral neck was treated.[5] In our own series, six of 37 patients (16%) had recurrence in the contralateral neck and none had received bilateral irradiation. The overall disease control rate in the contralateral neck, however, was 84%,

identical to the results of Reddy et al using bilateral irradiation. Treating the clinically negative neck with radiation also contravenes a basic rule that applies to any form of elective neck treatment. That is, it is not appropriate to electively treat the neck if the primary is not controlled. Contralateral irradiation is appropriate, therefore, if radiotherapy is also to be directed at the mucosal sites with a view to definitively treating the occult primary. We, therefore, reserve contralateral neck irradiation for cases of bilateral neck disease or those with a high suspicion of a nasopharyngeal primary.[1]

Radiation therapy – mucosal sites

Contralateral neck failure indicates the presence of active and, most likely, progressive mucosal disease. Failure in the contralateral neck should, therefore, prompt a thorough reevaluation of the patient, including focused physical examination, imaging, and endoscopy.

A principal area of controversy is whether or not to irradiate the mucosa, particularly the regions thought most often to harbor the occult primary lesion, i.e. nasopharynx, base of tongue, tonsil, and pyriform sinus. Opinions in the literature are divided, with similar results reported by those who include these sites and those who do not. Reddy and Marks reported that the likelihood of mucosal recurrence decreased significantly, if these mucosal sites were included in the radiation ports.[5] Similarly, Davidson et al found that mucosal recurrence declined with the inclusion of possible primary sites in the radiation fields as compared to earlier series in which this comprehensive radiation therapy was not routine.[2] Harper et al reported that the subsequent appearance of a primary cancer after neck and mucosal site irradiation was similar to the rate of metachronous second primaries following definitive radiation for known primary tumours.[14] They concluded that directing radiation to the neck and mucosal sites was, therefore, effective in treating the unknown primary lesion. Interestingly, they also found that the field and dose of radiation did not correlate with the incidence or pattern of mucosal recurrence, casting some doubt on their conclusion that the mucosal irradiation therapy had a measurable effect.[14]

A major argument against full mucosal irradiation is the substantial morbidity that follows treatment of the mucosal sites, particularly xerostomia.[1] Radiation to the nasopharynx tends to have the most profound effect in that regard. This, coupled with an inability to show any improvement in outcome in our own series, has prompted us to exclude the mucosa sites in the radiotherapy fields unless there is bilateral neck disease, as this portends a more aggressive tumour with a poor prognosis. However, when there is a clinical suspicion of a specific, though unproven, primary site, we will include radiation to that site.

Chemotherapy

Little has been written on the role of chemotherapy in the case of the unknown primary. Cisplatin and 5-fluorouracil (5-FU) have been used in varying combinations. de Braud et al reported a higher complete response rate and longer survival time with N3 disease when chemotherapy was added to the treatment regimen.[9,13] The number of patients reviewed was small, however, and the efficacy of chemotherapy, therefore, remains unproven in this setting.

Treatment Outcome

Ipsilateral neck control rates vary among series between 42% and 90%.[1–7,12,14,33] There is no apparent correlation with treatment regimen, however, with similar results reported for radiation and surgical therapies. The ipsilateral neck control rate in our series was 89%, using primarily

Table. Treatment outcomes

Author	*n*	Ipsilateral control	Contralateral control	Appearance of primary	Distant metastases	Disease-specific survival
McMahon[1]	37	89%	84%	14%	5%	63% at 4 years
Davidson[2]	73	74%	NR	12%	21%	60% at 5 years
Harper[14]	69	77%	NR	12%	NR	60% at 5 years
Maulard[4]	113	86%	NR	10%	16%	38% at 5 years

NR = not recorded.

a surgical approach with adjuvant irradiation reserved for N2 disease or greater. As previously stated, contralateral neck control varies between 80% and 90%.[1,5] A summary of outcomes is shown in the Table.

A primary site is eventually discovered in 10% to 30% of patients presenting with an occult primary cancer.[12,14,33] Generally, this occurs within 2 years of treatment, although later development of a primary has been described. It may be difficult to distinguish between the true unknown primary and an incidental second primary, the latter having an incidence of 3% per year following treatment of an initial primary lesion. In our own series, 5 of 37 patients (14%) eventually manifested a primary tumour. The most common primary sites, again, are the nasopharynx, base of tongue, tonsil, and pyriform sinus. Special mention should be made of level IV and specifically supraclavicular nodes, as these are associated with a primary in the chest in up to 30% of cases.[13]

Distant metastases are discovered in 5% to 40% of patients, usually within 2 years of treatment.[1–5,7] The most common sites are the lung and bone. Liver metastases also occasionally develop. There appears to be some correlation between the likelihood of distant spread and the stage of disease at presentation.

Disease-specific survival rates vary between 33% and 66% at 5 years.[1–7,14,33] Poor prognostic indicators include extracapsular spread, positive margins, and extent of disease at presentation.[1,2] Survival in our series was 63% at 4 years.

Overall Treatment Approach

Our approach to the unknown primary begins with a thorough history and physical examination including nasopharyngoscopy and directed palpation of the mucosal sites. A survey for skin lesions on the head and neck is also performed. The neck mass is then sampled using FNAB to give a histological diagnosis. The imaging study of choice is CT, with the PET scan under investigation and MRI reserved for difficult cases and patients with contrast allergy. Each patient then undergoes panendoscopy, including direct laryngoscopy and oesophagoscopy. The nasopharynx is routinely biopsied and the ipsilateral tonsil removed. Mucosa at the base of the tongue or hypopharynx is biopsied only if abnormal in appearance. At the same operation, a neck dissection to encompass the clinical disease and adjacent at-risk nodes is performed, with bilateral dissection as needed for bilateral disease. If the neck is pathologically N1, no further treatment is given. For N2 disease or greater, the ipsilateral neck is irradiated. If both sides of the neck are pathologically positive, or if there is a suspicion of a nasopharyngeal primary, both sides of the neck are irradiated along with the likely mucosal sites. Finally, the patient will be monitored closely for the next 5 years to check for the subsequent appearance of a primary cancer.

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