

Evidence based pathology: squamous carcinoma of the hypopharynx

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This best practice article reviews the published evidence on the pathology and patterns of spread of carcinomas of the hypopharynx, and the relevance of pathological features to prognosis. Medline (1966–2001) was searched using a combination of head and neck neoplasms and prognosis, focusing on hypopharynx and pathology. Other relevant publications were identified from the bibliographies of these papers, and from those obtained opportunistically. There is relatively little pathological literature devoted specifically to squamous carcinomas of the hypopharynx and most information comes from large series of patients with head and neck cancers at a range of sites. Lack of consistency in reporting and shifts in terminology make comparisons between series difficult. The most important features determining prognosis are size and extent of local spread of the primary carcinoma and extent of involvement of regional lymph nodes. There is evidence to support the use of the minimum dataset criteria for head and neck carcinomas at this site. Within the hypopharynx, subsite related differences in aetiology and biology may become important.

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METHODS

Published evidence was sought by a search of Medline (1966–2001) for papers referring to a combination of head and neck neoplasms and prognosis, focusing on hypopharynx and pathology. Other relevant publications were identified from the bibliographies of these papers, and from papers obtained from opportunistic reading of journals.

RESULTS

Epidemiology

Carcinoma of the hypopharynx is a relatively uncommon disease, which has an incidence of less than 1/100 000 of the population, and usually presents in patients aged 60–70 years.² Carcinoma of the piriform sinuses and posterior pharyngeal wall occurs mainly in men and is associated with alcohol and tobacco smoking. Postcricoid carcinoma is more common in women and is associated with sideropaenic dysphagia (Paterson–Brown–Kelly syndrome), leading to a wide variation in geographical incidence, being relatively more common in India, Iran, and Japan.³

A review of European cancer registry data suggests that within the group of patients with hypopharyngeal carcinoma, there is a higher proportion of piriform fossa carcinomas in France (78%), the Netherlands (63%), and the UK (53%) than in other European countries, such as Germany (18%) and Sweden (5%).⁴ Changes in incidence, diagnostic fashions, and referral pathways may have occurred over time, because in 1970 Harrison found 60% of hypopharyngeal carcinomas arising in the postcricoid region in his practice in London, UK.⁵ In the USA and Canada, 65–85% of hypopharyngeal carcinomas involve the piriform sinuses, 10–20% the posterior pharyngeal wall, and 5–15% the postcricoid region.⁶

Part of the apparent variation in prevalence of different primary subsites may arise from the tendency of carcinomas to involve more than one subsite at diagnosis; therefore, the allocation of a carcinoma to a putative site of origin may be an inexact science. Michaels⁷ noted that 60% of cases

The hypopharynx is formed by the right and left piriform sinuses (Latin “pirium” or “pear”), the posterior pharyngeal wall, and the postcricoid oesophagus,¹ each of which is regarded as a subsite of the hypopharynx for diagnostic coding. The mucosa is covered by non-keratinising stratified squamous epithelium and contains mucosal glands, scattered lymphoid aggregates, and a rich lymphatic plexus. Carcinomas arising in the hypopharynx are uncommon and are often considered to have a poor prognosis with a propensity to present with advanced primary disease requiring wider resection than carcinomas at other head and neck sites, and with a high risk of nodal metastasis.

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This paper is based on a presentation at a meeting on evidence based management of hypopharyngeal cancer organised by the National Otolaryngology Trials Office in November 2001. Further details and a full list of papers and references from this meeting can be obtained from the website www.noto.org.

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involved more than one site and usually all three areas are affected, with the piriform sinuses alone involved in 32%.

Macroscopic pathology of the primary carcinoma

Knowledge of the pathology and spread of hypopharyngeal carcinoma has come from elegant studies of whole organ sections⁷⁻⁹ which have been confirmed by imaging studies.¹ Because hypopharyngeal tumours tend to present at a relatively late stage, the early pattern of spread is more difficult to define than at some other head and neck sites.

Hypopharyngeal carcinomas are most often flat plaques with raised edges, and superficial ulceration. The carcinomas show a tendency for multisite involvement within the hypopharynx and extend into adjacent mucosal areas. The more extensive, multisite carcinomas tend to show superficial mucosal invasion and to be undifferentiated.³ The carcinomas tend to spread within the mucosa, beneath intact epithelium, for an average of 10 mm in the piriform sinus and 5 mm in the postcricoid region.^{5,8} Tumours spread through the muscle of the hypopharyngeal wall in most cases but the laryngeal cartilages resist invasion and are only invaded in a minority of cases.⁷

Superior spread of piriform sinus carcinomas often involves the lateral wall of the oropharynx and the base of the tongue. Carcinomas of the piriform sinuses, particularly those involving the medial wall, spread anteriorly into the supraglottic and glottic larynx. Once the paraglottic space is involved, the tumour may spread outside the larynx through the cricothyroid membrane. Vocal cord fixation may result from involvement of the crico-arytenoid joint, invasion of the posterior crico-thyroid muscle, or involvement of the recurrent laryngeal nerve.¹⁰⁻¹²

Posterior hypopharyngeal wall tumours tend to be exophytic and are often large (80% > 5 cm) at presentation,¹² extending into the posterior oropharyngeal wall.¹³ Postcricoid carcinomas tend to grow anteriorly to involve the posterior crico-arytenoid muscle, and may extend into the trachea through the cricoid cartilage or inferiorly to involve the oesophagus and trachea.⁵

The thyroid gland is often involved by hypopharyngeal carcinoma because of the proximity of the upper lobes to the lateral wall of the hypopharynx. Thyroid invasion is a poor prognostic factor.¹⁴

Microscopic pathology of the primary carcinoma

In situ carcinoma is often seen adjacent to invasive squamous carcinoma and, although there have been no studies of the preinvasive progression of hypopharyngeal carcinomas, a similar sequence to that seen in other head and neck sites is envisaged.^{15,16}

“Thyroid invasion is a poor prognostic factor”

The carcinomas are usually typical squamous carcinomas. The degree of differentiation varies, with undifferentiated carcinomas occurring more frequently in the piriform sinuses than in the oral cavity,¹⁷ although differentiation is apparently not related to biological aggression.⁷ In contrast to oral and laryngeal carcinomas,¹⁸ there are no detailed studies on the prognostic relevance of patterns of invasion at this site. Spindle cell and basaloid subtypes of squamous carcinomas occur in the hypopharynx. Basaloid carcinomas have a predilection for the tongue, piriform sinus, and supraglottic larynx, and have an aggressive behaviour, with a 64% incidence of cervical node metastasis and 44% rate of distant metastasis.¹⁹ Undifferentiated, lymphoepithelioma-like carcinomas are rare, and appear to have a similar behaviour and prognosis to typical squamous carcinomas. They are not associated with Epstein-Barr virus infection, tend to present in the 7th decade of life with early metastasis and, although radiosensitive, are not usually cured by radiotherapy alone.²⁰

Table 1 Distribution of nodal metastases

First author (ref)	Clinical node assessment	Pathological node assessment (% cases with positive nodes)		
		Level II	Level III	Level IV
Jones ²⁷	All patients	70%	23%	5%
Candela ²⁸	N0	15%	8%	0%
	N+	72%	72%	47%
Shah ²⁶	N0	75%	75%	0%
	N+	78%	75%	47%

Pathology of nodal metastases

Nodal metastasis is more common for hypopharyngeal primary carcinomas than for some other head and neck sites, although the frequency and pattern of metastasis varies according to the hypopharyngeal subsite.²¹ Delayed regional metastasis (more than two years after diagnosis) is more common for patients with piriform sinus carcinoma (31%) than for patients with postcricoid (18%), supraglottic (16%), or glottic (6%) carcinomas.²²

Even small (T1–2) piriform sinus carcinomas are associated with nodal spread at presentation¹⁰ and there is a high (> 50%) chance of occult nodal metastasis.^{23,24} Bilateral metastatic disease is common, and even in patients with a clinically N0 neck, 56% of ipsilateral and 47% of contralateral neck dissections contain positive nodes.²⁵

Piriform sinus carcinomas spread most often to level II nodes, with level III and IV nodes being involved particularly in clinically node positive patients (table 1). Eleven per cent of piriform fossa carcinomas have metastases in the supraclavicular nodes or posterior triangle.²⁶

Tumours of the posterior pharyngeal wall may also spread to retropharyngeal nodes in 40% of patients.²⁹ Postcricoid carcinomas spread to mid and lower cervical nodes and paratracheal nodes, and have a lower incidence (30%) of nodal metastasis than other hypopharyngeal carcinomas.²⁷ Eighteen per cent of patients have bilateral cervical node metastases.⁶

Only one paper specifically looks at the prognostic importance of extracapsular spread from nodal metastases in hypopharyngeal carcinoma. The relative risk for recurrence of neck disease is greater if the nodes are more than 3 cm in diameter and when macroscopic extracapsular spread is present.³⁰

Pathology of distant metastases

Distant metastases in the lungs, mediastinum, bone, liver, or skin develop in 20–40% patients within nine months of diagnosis, and survival is usually less than one year after these are detected.^{3,31} The incidence of distant metastases at presentation is higher for hypopharyngeal carcinomas (17–24%) than for all head and neck sites (11%).^{22,32}

Second primary carcinomas

The incidence of second primary carcinomas is probably less common in patients with primary hypopharyngeal carcinomas (5–6%) than for those with primary laryngeal carcinomas (9–13%).^{22,33} These data may be biased by the shorter survival of patients with hypopharyngeal carcinoma.

Molecular pathology

In most molecular biological studies, hypopharyngeal carcinomas are grouped with other sites. p53, angiogenesis related markers, cyclin D1, endothelial growth factor receptor, DNA ploidy and cell kinetic markers show promise as prognostic markers or as markers for potential therapeutic sensitivity,^{34,35} but none has yet proved useful for routine use.

Table 2 TNM staging⁴²

T1	Tumour limited to one subsite and 20 mm or less in greatest dimension
T2	Tumour involves more than one subsite or measures 21–40 mm in size
T3	Tumour >40 mm in size or with fixation of hemilarynx
T4	Tumour invades adjacent structures
pNX	Nodes cannot be assessed
pN0	No nodal metastasis
pN1	Metastasis in single ipsilateral node 30 mm or less in diameter
pN2	Metastasis in single ipsilateral node 31–60 mm diameter, or metastasis in multiple ipsilateral, bilateral, or contralateral nodes <61 mm diameter
pN3	Metastasis in lymph node more than 60 mm diameter

Multivariate analysis of histopathological features and DNA flow cytometry in piriform sinus carcinomas showed that the most important prognostic factors were tumour size, lymphatic invasion, and nodal status; ploidy contributed no additional prognostic information.³⁶

Higher cyclin D1 expression has been described in pharyngeal carcinomas but may not correlate with gene amplification.^{37–38} The expression of c-erbB2 is associated with a lower risk of distant metastasis,³⁹ and nuclear expression of β catenin may be a marker of poor prognosis.⁴⁰

There is little information about site specific chromosomal aberrations. A recent study using fluorescent in situ hybridisation showed gains or losses for most chromosomes in most head and neck cancer specimens. Loss of chromosomes 3 and 10 was most commonly seen in laryngeal carcinomas, loss of chromosome 9 in oropharyngeal carcinomas, and loss of chromosomes 11 and 18 in hypopharyngeal carcinomas.⁴¹

Staging and prognosis

The 1997 revision of the TNM staging system included, for the first time, size criteria for hypopharyngeal carcinomas (table 2).⁴² In an earlier revision, the stage criteria for the hypopharynx were defined by the involvement of one or more subsites. This may make it difficult to compare prognostic and staging data in clinical series reported at different times. The expansion of the anatomical descriptor of the posterior wall of the hypopharynx to include tumours down to the inferior border of the cricoid cartilage may also influence the interpretation of some studies.

Carcinomas of the hypopharynx have a worse prognosis than carcinomas of other head and neck sites, although prognosis varies between clinical series and anatomical subsites within the hypopharynx (table 3). The poor prognosis is thought to result from presentation at a late stage, multisite involvement within the hypopharynx, unrestricted soft tissue tumour growth, and the extensive mucosal lymphatic network promoting metastasis, together with the restricted surgical options for complete resection. In large series, 67% of patients have T3 or T4 carcinomas and 87% are stage III or IV at presentation.^{12–22} About 25% patients will present with a mass in the neck, and 70% will have nodal metastases at presentation.^{10–12, 27}

Table 3 Prognosis of patients with hypopharyngeal carcinomas

Clinical series (ref)	Anatomical site of carcinoma	Disease free 5 year survival
Spector <i>et al</i> (1995) ¹²	All hypopharynx	65%
Spector <i>et al</i> (2001) ²²	All hypopharynx	56%
Jones <i>et al</i> (1998) ⁴³	Piriform fossa	31%
Jones <i>et al</i> (1998) ⁴³	Postcricoid	29%
EURO CARE II project ⁴	All hypopharynx	22%
Jones <i>et al</i> (1991) ¹³	Posterior pharyngeal wall	18%

The main clinical prognostic factors are T and N stage, age, and performance status.^{12–13, 43} with the poor prognosis in many patients being related to their poor overall health. A recent study found that the presence or absence of nodal disease did not significantly affect prognosis, but that patients with a calculated total volume of metastatic disease of more than 100 cm³ had a worse prognosis.⁴⁴ A drop in survival after two years is the result of distant metastases and second primary malignancies.²² Carcinomas of the postcricoid region less than 5 cm long have a better survival than longer carcinomas, but carcinomas associated with vocal cord paralysis (implying spread outside the hypopharynx and involving the recurrent laryngeal nerve) have a particularly poor prognosis.¹⁴

Surgical margins and local recurrence

The question “what is an adequate surgical margin for resection of malignancy?” is one that may never be answered to the satisfaction of all surgeons, pathologists, oncologists, and patients. Pathological aspects of the assessment of surgical margins of head and neck carcinomas have been reviewed.⁴⁵ For carcinomas of the upper aerodigestive tract there is site specific variation in the likely biological relevance of marginal involvement that relates less to histological differences in carcinomas, and more to the surgical anatomy, and to the biological and epidemiological environment of the sites.

“Most papers suggest that surgical margins should be wider for resections of hypopharyngeal carcinoma because the rate of local recurrence is greater than for carcinomas at other sites”

Pathologists are well aware of the effects of formalin fixation, tissue processing, and sectioning on absolute measurements of the size of tissues. The scale of the problem, and an indication of the complexity of clinicopathological discussion, is provided by a study of oral resection specimens in which a minimum average surgical margin of 10 mm was measured at 5.4 mm in tissue sections.⁴⁶

Most papers suggest that surgical margins should be wider for resections of hypopharyngeal carcinoma because the rate of local recurrence is greater than for carcinomas at other sites.^{5–8} The data supporting this idea are limited by inconsistency in the criteria used to record margins (“tumour free” margins may show dysplastic changes), anatomical restrictions of surgery, and the use of adjuvant treatment. A practical view is based on the evidence that for the oral cavity and pharynx, any lesional tissue (in situ or invasive carcinoma) within 5 mm of a surgical margin is associated with an 80% incidence of recurrent disease.⁴⁵ This is supported by Looser *et al* who, using similar criteria, found local recurrence in 71% of patients with head and neck carcinoma who had positive margins and 32% of patients with negative margins.⁴⁷ The incidence of positive margins is higher in cases with larger tumours and this is associated with higher incidences of local, regional, and distant failure.⁴⁵

Take home messages

- Carcinomas arising in the hypopharynx are uncommon and are often considered to have a poor prognosis with a propensity to present with advanced primary disease requiring wider resection than carcinomas at other head and neck sites, and with a high risk of nodal metastasis
- Little pathological literature is devoted specifically to squamous carcinomas of the hypopharynx and most information comes from large series of patients with head and neck cancers at a range of sites
- A general lack of consistency in reporting and shifts in terminology make comparisons between series difficult
- The most important features that determine prognosis are the size and extent of local spread of the primary carcinoma and the extent of involvement of regional lymph nodes. There is evidence to support the use of the minimum dataset criteria for head and neck carcinomas at this site
- Within the hypopharynx, subsite related differences in aetiology and biology may become important

Molecular techniques have the potential to define marginal status more objectively, but are not yet suitable for routine use.⁴⁸ Brennan *et al* found a high recurrence rate when p53 mutations were identified in tissue from the margins of resected head and neck carcinomas, although this technique is only useful if the primary carcinoma shows a p53 mutation.⁴⁹ There are several different reasons why p53 abnormalities may be present in apparently normal mucosa, only some of which may be related to the recurrence or development of second primary tumours. The mRNA translation initiation factor, eIF4E, is consistently present at an increased concentration in squamous carcinomas. Western blotting and immunohistochemical evidence of eIF4E positivity at excision margins is associated with a higher rate of local recurrence and a shorter disease free survival.⁵⁰

Practical relevance

The diagnostic pathologist is required to make a diagnosis that is supplemented by information that will assist the surgeon and oncologist in providing prognostic information for the patient and which may guide adjuvant treatment. The pathological data relating specifically to hypopharyngeal carcinoma are more limited than for other head and neck sites,⁵¹ but the general principles of a clear description of the macroscopic pattern of primary and metastatic disease, confirmed histologically, are maintained. There is published evidence to support the recording of most of the data items in the *Minimum dataset for head and neck cancer*,⁵² and it is to be hoped that a consistent approach to the recording of other data will allow the importance of these features to be assessed accurately in the future.

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