Pain and dysphagia in patients with squamous carcinomas of the head and neck: the role of perineural spread[1]

R L Carter DM FRCPath
M R Pittam MA FRCS[2]
N S B Tanner MA FRCS[3]
Department of Pathology and Head and Neck Unit
Royal Marsden Hospital and Institute of Cancer Research, London and Sutton

Summary: Clinical and pathological features of perineural spread have been investigated in patients with squamous carcinomas at several sites in the head and neck. In 100 surgical cases, the clinical and pathological findings were congruent in 76%. Combined clinical and histological evidence of perineural invasion was recorded in 33% and the overall incidence of nerve involvement detected morphologically was 44%. Perineural infiltration was demonstrated histologically in 51% of major excisions from the buccal cavity and in 34% of resections from the oropharynx, hypopharynx and cervical oesophagus. The neurological findings were dominated by hypoaesthesia, dysaesthesia and referred pain – mainly in the territories of cranial nerves V and IX. Multiple and/or sequential nerve involvement was occasionally seen. No correlation was established between nerve invasion and metastasis to regional lymph nodes. Long-distance infiltration of nerve trunks, and multiple involvement, are grave prognostic features.

In 17 terminal patients submitted to autopsy, 65% had combined clinical and pathological evidence of perineural spread and the overall incidence of nerve involvement detected morphologically was 88%. Sensory changes again predominated. Multiple nerve involvement was observed in 35%. An apparently new 'dysphagia syndrome' is described in 4 patients with oropharyngeal carcinomas in whom gross mechanical obstruction was simulated by a combination of perineural spread of tumour into the ipsilateral vagal trunk, sometimes accompanied by segmental infarction, variable invasion of the sympathetic chain, and 'splinting' of the pharynx by local fibrosis and tumour in the soft tissues of the neck. Short-term palliation was achieved in these patients with high-dose steroids.

Introduction

Squamous carcinomas of the head and neck arising from mucosal surfaces tend to ulcerate superficially, infiltrate underlying tissues and eventually metastasize to regional lymph nodes in the neck. The symptoms produced depend on the site and size of the tumour, the extent of deep invasion and the nature of the tissues involved. Pain and dysphagia are common features and, in many instances, are attributable to local effects such as ulceration, infection and obstruction which are (for the most part) easily explained. Other effects may, however, be more subtle. Infiltration of perineural spaces is a well recognized mode of tumour spread (Willis 1973) which, in the head and neck region, is particularly associated with adenoid cystic carcinomas of the salivary glands. It also occurs in squamous carcinomas arising in this region (Ballantyne *et al.* 1963, Dodd *et al.* 1970) and it now appears that perineural spread is commoner in this group of cancers than was previously thought: investigations from the

[1] Based on paper read to Section of Oncology, 14 April 1982. Accepted 18 May 1982
[2] Present address: Surgical Unit, Westminster Hospital, London SW1 2AP
[3] Present address: Department of Plastic Surgery, Canniesburn Hospital, Bearsden, Glasgow
Reprint requests to RLC, Haddow Laboratories, Royal Marsden Hospital, Sutton, Surrey

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Royal Marsden Hospital indicate that perineural invasion is present in about 25% of all major surgical resections from patients with squamous carcinomas of the head and neck, and that clinical and pathological evidence of nerve involvement is congruent in about two-thirds of cases (Carter *et al.* 1979, Carter & Pittam 1980). Such close correlation is largely due to the fact that dysfunction in certain nerves in the head and neck is somewhat easier to recognize clinically than at other sites.

This paper summarizes our combined clinical and pathological experience of perineural spread by squamous carcinomas of the head and neck in a large surgical series and in a smaller series of terminal cases. The two groups are essentially complementary. In the surgical series, preoperative clinical assessment is fairly simple but morphological correlation is limited by the extent of the surgical procedure. In the terminal group, clinical evaluation is sometimes difficult – because the patients are very ill, they have massive local disease often with sepsis, and they have been previously treated by surgery and irradiation – but pathological correlation is easier because more detailed dissections can be made. Data are presented for primary tumours from two principal groups of anatomical sites – the buccal cavity and the oropharynx, hypopharynx and cervical oesophagus. A few neoplasms in the nose and paranasal sinuses are also included. Tumours arising in the larynx have been omitted because a separate study has shown that clinical and pathological correlation of perineural spread is poor at this site (Pittam & Carter 1982).

Patients

Patients in the surgical series were admitted to the Royal Marsden and King's College Hospitals; most of the patients in the terminal groups were admitted to St Christopher's Hospice. Thorough medical histories were taken and neurological examinations were made. Standard ENT investigations were carried out on the surgical patients and on most of the terminal cases to exclude coexisting sepsis and other unrelated diseases. Surgical specimens and autopsy tissues were dissected in detail, fixed and processed by standard techniques for histopathology, and examined by one of us (RLC) without knowledge of any neurological changes previously detected by the other two authors (NSBT or MRP).

Results

Surgical series

A group of 100 patients was investigated, consisting of 75 men aged between 26 and 74 years (mean 57) and 25 women aged between 34 and 86 years (mean 62). The sites of the primary tumours are listed in Table 1. All patients presented with T_2, T_3 or T_4 tumours, and all of them received radiotherapy and/or chemotherapy before major surgery. Eighty-six patients were given preoperative irradiation, usually to doses of 4000 to 6000 rads. Surgery was subsequently undertaken because the primary tumour had recurred locally or had failed to respond to previous treatment.

The occurrence of perineural spread, assessed clinically and pathologically in these patients, is summarized in Table 2. 'C' and 'P' denote clinical and pathological evaluation of nerve involvement, and the results in each category are recorded as positive (+) or negative (−). When the group is considered as a whole, it is seen that clinical and pathological results were concordant in 76% of cases: i.e. C−P− 43% and C+P+ 33%. Discordant results in the remaining 24% were distributed almost equally between C+P− 13% and C−P+ 11%. The incidence of perineural spread described clinically and pathologically in this series was 33%, and the total incidence of nerve involvement, detected pathologically, was 44%: i.e. C+P+ 33% and C−P+ 11%. The results in Table 2 are also analysed with respect to the site of the primary tumour. The two principal groupings comprise tumours arising in the buccal cavity, and those in the oropharynx, hypopharynx and cervical oesophagus. In the first group, clinical and pathological findings were congruent in 79%. C+P+ cases made up over one-third of the total. Pathological evidence of perineural spread was found in 51% of major surgical resections from this group: i.e. C+P+ 37% and C−P+ 14%. In the second group,

Table 1. Sites of primary tumours in surgical series

	No. of patients
Buccal cavity	61●
Oropharynx, hypopharynx, cervical oesophagus	29
Nose, paranasal sinuses	8
Miscellaneous	2■

● Tongue 39; floor of mouth, retromolar trigone and alveolus 18; buccal mucosa 3; lip 1
■ One each in external auditory meatus and lacrymal sac

clinical and pathological findings were congruent in 66% but the incidence of perineural spread was lower: 34% (C+P+ 24% and C−P+ 10%). The proportion of patients with suggestive clinical evidence of nerve involvement, unconfirmed by subsequent pathological examination (C+P− 24%), suggests that clinical evaluation may be less reliable in this region than in the buccal cavity.

The clinical patterns of perineural spread, summarized according to the anatomical site of the primary tumour, are shown in Table 3. The principal group comprises 33 patients with combined clinical and pathological evidence of invasion of nerve trunks (C+P+). All the cases showed sensory changes, with local or referred pain, paraesthesia or anaesthesia in 26 (79%). Synchronous sensory and motor deficits were present in 4 patients, involving the trigeminal and facial nerves, and one of these cases went on to develop an ipsilateral abducent nerve palsy. Three of the patients died within 8 months with presumed intracranial extension, but autopsies were not performed. A smaller group of 13 patients presented symptoms and signs of nerve involvement which were not confirmed histologically (C+P−). The neurological findings were exclusively sensory; 4 out of 5 patients with carcinomas of the hypopharynx complained of referred pain to the ear, suggesting infiltration of the vagus.

The association between perineural spread and metastasis to regional lymph nodes was examined in patients with tumours in the buccal cavity and in the oropharynx, hypopharynx

Table 2. Clinicopathological correlation of perineural spread according to sites of primary tumours in 100 patients submitted to major surgery

	No. of patients	Clinicopathological correlation ●			
		C−P−	C+P−	C−P+	C+P+
Buccal cavity	61	26 (42%)	4 (7%)	8 (14%)	23 (37%)
				51%■	
Oropharynx, hypopharynx, cervical oesophagus	29	12 (42%)	7 (24%)	3 (10%)	7 (24%)
				34%■	
Nose, paranasal sinuses	8	4 (50%)	2 (25%)	0	2 (25%)
Miscellaneous	2	1 (50%)	0	0	1 (50%)
Overall results	100	43	13	11	33
				44%■	

● See text for explanation of symbols
■ Pathological demonstration of perineural spread

Table 3. Clinical patterns of perineural spread according to site of primary tumour in patients in surgical series

	Neurological disturbance		
	Sensory	Sensory and motor	Nerves involved●
Clinical and pathological evidence of nerve involvement (C+P+, n=33):			
Buccal cavity	21	2	V (21) V+VII (2)
Oropharynx, hypopharynx, cervical oesophagus	7	0	IX (6) X (1)
Nose, paranasal sinuses	1	1	V (1) V+VII→VI (1)
Miscellaneous	0	1	V+VII (1)
Clinical evidence not confirmed pathologically (C+P−, n=13):			
Buccal cavity	4	0	V (4)
Oropharynx, hypopharynx	7	0	IX (3) X (4)
Paranasal sinuses	2	0	V (2)

● Figures in parentheses denote numbers of patients
V: Mandibular division of trigeminal nerve principally involved
VII: Motor defects principally affect facial branches; involvement of VII within facial canal or at stylomastoid foramen was not seen. Sensory function of VII could not be reliably appraised
IX: Sensory function only assessed; motor function of IX could not be reliably appraised
X: Sensory involvement mainly recognized by referred otalgia; motor function of X could not be reliably appraised

and cervical oesophagus (Table 4). No consistent relationship emerged in either group, though the occurrence in 11 patients with tumours of the buccal cavity of perineural spread without nodal metastases is interesting.

The morphological features of perineural infiltration may be summarized briefly. Tumour cells invade the perineural spaces and may spread along them, extending both centrally and peripherally. The cells remain concentrated at the margins of the involved nerve trunks and show little tendency to infiltrate inwards into the substance of the nerves (Figure 1). It is, however, now clear that the fibres in involved nerves are frequently damaged. There appears to be a progressive loss of myelin and axon components, probably due to regional ischaemia (*see* Discussion). Actual segmental infarction of an involved nerve was demonstrated in one patient in this surgical series, and 3 more examples have been encountered in the autopsy dissections which are described later.

Terminal and autopsy series

A group of 17 patients was investigated, comprising 13 men and 4 women aged between 50 and 95 years (mean 67). The sites of the primary tumours were: buccal cavity (6), oropharynx

Table 4. Distribution of perineural spread and metastases to regional lymph nodes: surgical series

Site	LN+NE+	LN+NE−	LN−NE+	LN−NE−
Buccal cavity ($n=61$)	20	12	11	18
Oropharynx, hypopharynx, cervical oesophagus ($n=29$)	10	8	2	9

LN, lymph node; NE, nerve

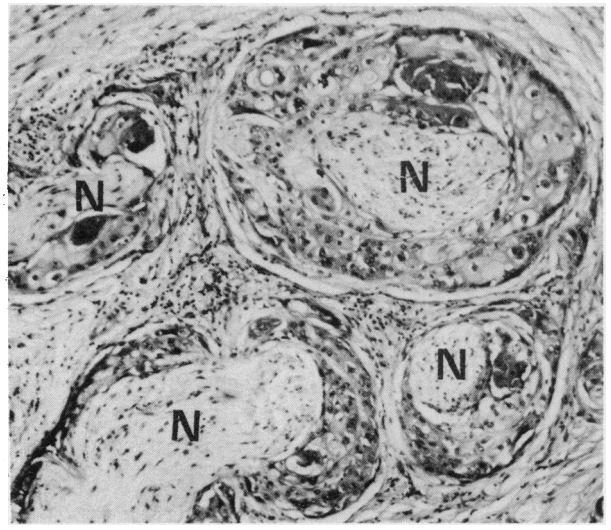

Figure 1. Squamous carcinoma of the tongue. Poorly differentiated tumour cells are infiltrating the perineural spaces of four nerve bundles (N). The nerve fibres are, for the most part, intact (cf. Figure 2) though special stains demonstrated focal axonal and myelin degeneration. The patient complained of severe pain in the mandibular division of V. (H & E ×90)

and hypopharynx (10) and nasal septum (1). Almost all the patients had advanced disease with primary and/or metastatic tumour which had previously been treated by permutations of surgery and/or irradiation, with or without chemotherapy.

The incidence of perineural spread, assessed clinically and pathologically in these patients, is summarized in Table 5. Comparison of results with the larger surgical series is not feasible, but it is clear that the overall incidence of perineural spread in these cases, submitted to autopsy examination, is extremely high: 15/17, 88%.

The clinical patterns of perineural spread in the series are shown in Table 6. Sensory disturbances again dominated the findings and there appeared to be a tendency for multiple sensory deficits to develop. Symptoms suggesting invasion of the cervical plexus were observed in 4 patients. The most striking finding was the occurrence of an unusual dysphagia syndrome in 4 out of 8 patients with advanced carcinomas of the oropharynx. These cases presented with total or near-total dysphagia for solids and liquids (including saliva) which was

Table 5. Clinicopathological correlation of perineural spread according to sites of primary tumours in 17 terminal patients at autopsy

	No. of Patients	Clinicopathological correlation			
		C−P−	C+P−	C−P+	C+P+
Buccal cavity	6	0	0	2	4
Oropharynx, hypopharynx	10	0	2	2	6
Nose	1	0	0	0	1
Overall results	17	0	2	4	11
				15 (88%)●	

● Pathological demonstration of perineural spread

Table 6. Clinical features of perineural spread according to primary site of tumour in patients in terminal series

	Neurological disturbance		
	Sensory	Sensory and motor	Nerves involved●
Clinical and pathological evidence of nerve involvement (*C*+*P*+, n=*11*):			
Buccal cavity	4	—	V (1); V+IX (1); V+IX+cervical plexus (1); V+cervical plexus (1)
Oropharynx, hypopharynx	5	1	IX (3); V+IX (2); V+VII+IX+XI+cervical plexus (1)
Nose	1	—	V (1)
Clinical evidence not confirmed pathologically (*C*+*P*−, n=*2*):			
Oropharynx, hypopharynx	1	1	IX (1); V+VII (1)

● Figures in parentheses denote numbers of patients
Comments on testing cranial nerves V, VII, IX and X shown in Table 3 also apply here

initially attributed to simple mechanical obstruction by a large mass of primary and/or metastatic tumour. The findings at autopsy indicated a more complex state of affairs (Table 7). Direct obstruction by local tumour was minimal or absent, and the dysphagia in these patients appeared to be due to a combination of factors – notably mechanical 'splinting' of one side of the pharynx by local fibrosis and tumour in the soft tissues of the neck, and perineural spread into the ipsilateral vagal trunk, sometimes accompanied by segmental infarction; the sympathetic chain was invaded in two instances (*see* Figure 2). These changes were exclusively unilateral, and bilateral infiltration of the vagus or sympathetic chain was never seen. The main trunk of the glossopharyngeal nerve was intact in all 4 cases.

The general histopathological characteristics of perineural spread were similar to those described in the surgical series but two additional observations were made in the autopsy material. Detailed dissections of nerve trunks showed segmental infarction associated with perineural infiltrates in the inferior dental nerve (1 case) and in the vagus (2 cases; see Table 7). Secondly, perineural spread was shown to be confined to the terminal 1 cm of the involved nerves in most patients. Long-distance centripetal spread of tumour was not seen.

Table 7. 'Dysphagia syndrome' in 4 men with advanced carcinomas of the oropharynx: autopsy findings

	PC (age 65)	LH (age 73)	AJ (age 50)	KB (age 57)
Lumen of pharynx narrowed by local tumour	No	No	Slightly	No
Spread of tumour into soft tissues outside pharynx	+	+	+	+
Cervical lymph nodes replaced by metastases	+	+	+	+
Fibrosis in cervical soft tissues	+	+	+	+
Perineural infiltration of vagus	+	+	+	Apparently obliterated in region of stylomastoid foramen
Infarction of vagus	+	−	+	
Infiltration of sympathetic chain	+	+	+	−

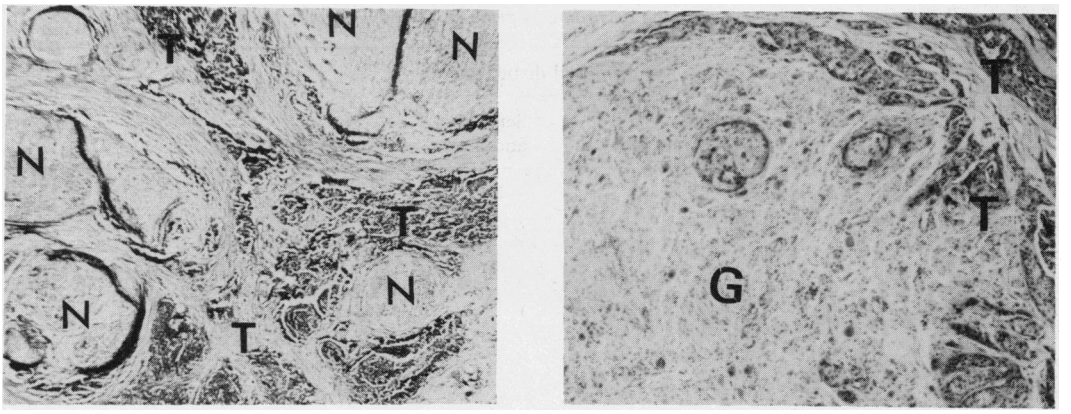

Figure 2. Morphological findings in patients with advanced squamous carcinomas of the hypopharynx and the 'dysphagia syndrome'. LEFT: Low-power view of the vagus nerve. Five nerve bundles (N) are completely necrotic (cf. Figure 1). Darkly staining tumour cells (T) are seen in perineural spaces and in connective tissues between nerve bundles. There is considerable local fibrosis, almost certainly as a result of previous irradiation (H & E ×35). RIGHT: A sympathetic gangion (G) invaded by squamous carcinoma (T) (H & E ×60)

Discussion

This combined investigation of patients in two surgical and terminal series has again demonstrated that there is a high incidence of perineural spread from squamous carcinomas at certain sites in the head and neck, and that clinical and pathological correlations are tolerably close. Certain differences between the surgical and terminal series were stressed earlier, and there are some general features which should be noted before the results are discussed. The clinical recognition of nerve involvement raises various points. Rigid criteria were adopted to identify nerve invasion. In assessing sensory defects, care was taken to exclude extensive local sepsis. Motor defects were often difficult to evaluate in patients with extensive tumours and fibrosis associated with previous irradiation – particularly for cranial nerves V, IX, X, XI and XII. The pathological recognition of nerve invasion was straightforward. Possible confusion of a focus of perineural spread in the oral cavity with local neuroepithelial embryological remnants such as the juxta-oral organ of Chevitz (Tschen & Fechner 1979) was borne in mind. More importantly, the high incidence of perineural spread reported in this study may in part reflect our practice of regularly taking at least 4 to 6 tissue blocks – and sometimes many more – for histology from each tumour.

In the surgical series, the incidence of histologically-confirmed perineural spread is most striking in patients with squamous carcinomas in the buccal cavity. Perineural invasion was detected in resected specimens from just over half the cases, nearly three-quarters of whom had clinical features suggesting nerve involvement preoperatively. Sensory changes in the territory of the trigeminal nerve were the main clinical findings, usually consisting of a combination of impaired or altered sensation in one segment or division and referred pain clearly localized to the jaw, side of the face or the forehead. Motor dysfunction in the trigeminal nerve attributable to perineural spread was not demonstrated in this series, and it appears that changes such as trismus are due to direct invasion by tumour. Perineural spread was less often encountered in patients with carcinomas of the oropharynx, hypopharynx and cervical oesophagus. Sensory changes again dominated the clinical picture with glossopharyngeal pain characteristically extending behind the angle of the jaw and felt deeply in the throat, sometimes radiating to the ear, and made worse by swallowing. The prognostic significance of perineural spread in our surgical patients is not entirely clear-cut. Three of the 4 cases with evidence of invasion of more than one cranial nerve died within 8 months with presumed intracranial extension of their tumours, but two points should be noted. Long-distance spread of carcinoma cells along perineural spaces is uncommon in this series, and no

consistent association has emerged between perineural invasion of one nerve trunk and the major prognostic determinant – the presence of metastasis in regional lymph nodes. On the other hand, perineural spread may provide the only evidence of potential distant invasion: the significance of trigeminal nerve dysfunction (in particular) has been emphasized throughout this paper, and such evidence merits careful consideration when planning treatment. Secondly, the prognostic implications of perineural spread vary from one site to another within the head and neck, and the broad grouping of sites used here may obscure differences within them (cf. Carter & Pittam 1980).

In the terminal series, the incidence of verified perineural spread was extremely high. Sensory changes again predominated. Multiple nerve involvement was more common, reflecting the large size of the tumours present. The most important conclusion to emerge is the preliminary identification of an apparently new dysphagia syndrome in patients with advanced carcinomas of the oropharynx. The clinical picture is one of complete or near-complete mechanical blockage; but pathological observations indicate that there is little or no direct obstruction and that the symptoms and signs are due to a combination of local changes with a large neurological component. Neoplastic infiltration of the ipsilateral vagal trunk (sometimes with infarction), and coexisting invasion of the sympathetic chain, are the most striking features; but unilateral 'splinting' of the pharynx by local fibrosis and tumour in the soft tissues of the neck is also a consistent finding. The recognition of such cases is important, as a measure of effective short-term palliation has been achieved here with dexamethasone 8 mg/day intramuscular or oral. The basis for the dysphagia is clearly complex and is likely to involve a sizeable element of neuromuscular incoordination. Detailed radiological investigations to pursue this point are, however, wholly inappropriate in such patients.

The morphological features of perineural invasion have been reported previously (Carter *et al.* 1979, Carter & Pittam 1980). The autopsy series described here has provided an opportunity to examine the distances which perineural tumour may traverse. The results so far indicate that perineural tumour tends to remain localized within the terminal 1 cm of the involved nerves. Further spread may be impeded by the dense local fibrosis, usually radiation-induced, which is commonly found in these patients. A few examples of more distant infiltration were seen in the surgical series, notably with tumour extending peripherally from the buccal cavity down the inferior dental nerve. One patient with a squamous carcinoma of the external auditory meatus was found in his petrosectomy specimen to have perineural infiltration in the nerves to the sphenopalatine ganglion – a distance of about 6 cm. More distant perineural spread has been reported by Ballantyne *et al.* (1963). Further examples have now been seen of infiltrated nerves showing regions of segmental infarction. Such changes have been observed in nerves enclosed within confined spaces, such as bony canals, and also in soft tissue albeit densely fibrotic from previous irradiation; compression of segmental blood vessels by infiltrating tumours seems to be the likely mechanism. The regular occurrence of axonal and myelin degeneration in infiltrated nerves is also confirmed, conflicting with older investigations which suggested that infiltrated nerves remained intact (Willis 1930, 1973). Some correlations can be drawn between structural alterations in nerve fibres and certain neurological changes observed, such as regional anaesthesia, hypoaesthesia, dysaesthesia or paresis; but the anatomical basis for referred pain in these cases remains obscure. It should finally be emphasized that several factors may combine with perineural infiltration to produce some of the neurological changes observed here. Local fibrosis, usually associated with radiotherapy, is an important component in the dysphagia syndrome, and perineural fibrosis may occasionally be associated with severe pain in the absence of detectable local tumour; 4 examples of such changes at the sites of previous caesium implants in the tongue have recently been examined by us.

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