

Pain Preceding Recurrent Head and Neck Cancer

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Over a 7-year period, 12 patients experienced recurrence of primary head and neck cancers preceded by severe orofacial pain. Pain began within 6 months following treatment in 10 of 12 patients and was progressive in 11 of 12 patients. Six patients died from recurrence, five within 2 years following onset of pain. No clear indication of malignant disease was evident despite clinical examination, plain radiography, magnetic resonance imaging, and computed tomography. Pain was often mistaken for denture irritation. Frequently, no area of irritation was apparent.

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Intense orofacial pain in posttreatment head and neck cancer patients may precede and indeed herald recurrent disease. Presenting signs and symptoms of primary head and neck cancer may vary. Carcinoma in situ of the oral cavity has been discovered because of local pain.¹ Patients also present when dentures fit poorly, a growth is discovered, or a discolored patch is visible.²

In a review of 52 patients with histologically confirmed carcinoma of the pharynx, Epstein and Jones et al³ reported pain as a presenting symptom in 46%. In an earlier study, Epstein and Stewart⁴ estimated the prevalence of pain associated with oropharyngeal cancer at 82%. In these studies, pain initiated headache or earache and was described as "dull" or "pressing" in nature.

Cancer of the maxillary sinus can cause nasal obstruction,^{2,5} epistaxis,^{2,5} facial swelling, and facial pain. Pain was found to be the primary symptom in squamous cell carcinomas of the larynx by Laccourreye et al.⁶ Pain was described as a sore throat by 32% of patients, as otalgia by 28%, and as odynophagia by 23%.⁶

Occult parotid adenoid cystic carcinoma has a propensity for infiltration of nerves and, consequently, neurologic symptoms including pain are frequently evident.⁷ Symptoms may include localized or radiating tenderness.⁷ Other parotid carcinomas may induce radiating pain to the mastoid area and periodontal pain.⁸

Pain therefore is a common symptom in almost all types of head and neck cancer. Discomfort of some sort is the primary reason patients seek care.⁴ Intuitively, a recurrent tumor would be

expected to exhibit the same signs and symptoms as the primary tumor. In reviewing the literature, this suggestion seems to hold true. Recurrent tumors have been documented to spread perineurally and to cause neurologic disruption and destruction of surrounding structures.⁹

Pain frequently accompanies recurrent tumors. Metheltraut and Brown¹⁰ described glossopharyngeal neuralgia accompanying recurrence. When pain is severe and progressive in magnitude, one must always be suspicious of recurrent tumor.¹⁰ In a study by Jones et al,¹¹ patients with varying cancer types were surveyed as to their quality of life and functional capacity. Patients with recurrent cancers reported a poorer quality of life and reported the highest frequency of pain.

Recurrence rates for various head and neck cancers reported in the literature vary widely. The consensus is approximately 25% for squamous cell carcinomas (SCCs) of the upper aerodigestive tract (Table 1). Pinto and Jacobs¹² put local or regional recurrence at 66% for SCC of the head and neck, the majority of which recur within 2 years.

At the authors' institution, a large number of head and neck cancer patients (in excess of 400 new patients per year) obtain care at one facility. Consequently, encounters with and observation of patients with recurrent disease is frequent. Over a period of 7 years, it has been noted by the authors that a number of patients with locally recurrent disease present with (among other signs and symptoms) severe, unrelenting orofacial pain. Prior to histologic confirmation of recurrence, no evidence of malignant neoplasm was detectable.

Few studies have dealt specifically with the etiology of pain in head and neck cancer patients.¹³ Even fewer have specifically examined the character and circumstances associated with pain as related to recurrent cancer. The purpose of this study was to examine patients with orofacial pain and associated local recurrence to discern common characteristics such as pain site, quality, and other characteristics.

Materials and Methods

Only patients with primary and recurrent oral cancers (those involving the lip, tongue, salivary glands, floor of mouth, oropharynx, nasopharynx, and other¹³) (ICD-9140-149¹³), laryngeal cancers, or lymphomas were considered.

The patient database was initially compiled from the entire patient listings of the Department of Dentistry, Princess Margaret Hospital, Toronto, Canada. The listings were sorted according to data

Table 1 Reported Recurrence Rates of Head and Neck Cancers

Study*	Recurrence rate (%)	N	Time (y)
1. Anderson et al ¹	57	22	3
2. Dobrowsky et al ⁹	33	70	1.5
3. Housset et al ⁸	27	23	Unknown
4. Kramer et al ²¹	23	320	4
5. Laccourreye et al ⁶	63	22	3
6. Marcus et al ²²	25	65	2
7. Peters et al ²³	25	200	2
8. Vikram et al ²⁴	15	114	2
9. Zelefsky et al ²⁵	20	75	7

*Type of cancer:

1. Malignant melanoma of the respiratory tract or oral cavity.
2. SCC of the oral cavity, oropharynx.
3. Isolated recurrent cervical lymphadenopathy from previous ENT carcinomas.
4. SCC of the oral cavity, oropharynx, supraglottic larynx, or hypopharynx.
5. SCC of the arytenoid.
6. SCC of the oral cavity, oropharynx, larynx, supraglottic larynx, and pyriform sinus.
7. SCC of the oral cavity, oropharynx, larynx, hypopharynx.
8. SCC of the oral cavity, oropharynx, larynx, hypopharynx.
9. SCC of the oral cavity, oropharynx.

pertaining to postcancer treatment complications. Patients specifically complaining of pain were noted. Dental and medical charts were reviewed in their entirety for this particular group. Patients who had documented local recurrence were grouped together.

A database record was formulated to evaluate these patients. The following data were compiled from patients with reports of pain and documented recurrence:

- Patient name, age, hospital number, race, and sex
- Initial (provisional) diagnosis of primary tumor
- Initial symptoms of primary tumor
- Primary tumor type, stage, site, and initial treatment modality
- Investigations performed to arrive at the diagnosis for the primary tumor
- Recurrent tumor site
- Time from diagnosis of primary to onset of pain
- Time from pain to confirmation of loco-regional recurrence
- Time from completion of treatment for primary to confirmation of recurrence
- Time from pain to treatment for recurrence
- Time from pain to death (if that is the final outcome)
- Time from diagnosis of primary to completion of treatment for that tumor
- Time from diagnosis of recurrence to completion of treatment for recurrence
- Number of dental appointments with complaint of pain related to recurrent tumor

Table 2 Ages of Patients by Sex

Sex	Ages (y)	Average (y)
Female (n = 7)	49, 52, 62, 64, 67, 69, 87	64.3
Male (n = 5)	49, 56, 57, 68, 90	64.0
Overall (n = 12)	Range 49-90	64.1 (median = 62)

- Patient's description of pain site(s), quality, severity, and changes in severity
- Other signs and symptoms present concomitantly with pain
- Medication being taken for pain relief
- Investigations undertaken to diagnose recurrence
- Treatment modality for primary cancer
- Treatment modality for recurrence

The database record was applied to all patients previously grouped together by their common characteristics of orofacial pain preceding recurrent malignancy.

Patients' ages were calculated from their dates of birth and reflected their age at death (if this occurred). The first diagnosis, based on signs and symptoms arising from the primary cancer, was recorded under the heading "initial diagnosis." This may or may not have recognized malignancy as the source of signs and symptoms. Investigations that aided diagnosis of either recurrent or primary tumors included magnetic resonance imaging (MRI) scans, computed tomography (CT) scans, and clinical and radiologic examinations. Time spans between various processes (eg, time between pain onset and recurrence) were calculated from dates recorded in medical and dental records. Dates of diagnosis for primary and recurrent cancers were taken to be the date of histopathologic confirmation.

Pain was only recorded if it had no obvious non-malignant etiology. For example, dental pain attributable to obvious caries or recent extraction was not included, nor was pain secondary to denture irritation accompanied by clinical signs. If pain persisted after these potential causes were eliminated, however, the pain attributes were included. The number of dental appointments at which pain was reported by the patient only included those at which the dentist recorded the patient's complaint. Consequently, the recorded number is likely an underestimate of pain duration.

A total of 12 patients were entered into the study. Their ages ranged from 49 to 90 years (mean 64.1, median 62) (Table 2). All patients in the study group had received care for their primary cancers between February 1988 and March 1995

at the authors' institution. Seven patients were women, five were men. All 12 patients were white.

Results

All cancers were squamous cell carcinomas. Nine patients had primary tumors of the oral cavity or pharynx. Three presented with cancer of the maxillary sinus, larynx, and ear, respectively. Specific locations and staging of primary tumors are listed in Tables 3a and 3b.

Ten of 12 patients had a correct provisional diagnosis of SCC. One patient with SCC of the ear canal was originally diagnosed as having a chronic ear infection and was treated with antibiotics. One patient with SCC of the left alveolus was initially diagnosed as having a symptomatic third molar and subsequently had it extracted.

The average time from completion of therapy for the primary tumor and recurrence-related pain was 20 weeks (median 11 weeks). Ten of 12 patients had pain within 7 months (median 6 months) following completion of treatment for their primary cancer.

Confirmation of recurrence followed the onset of pain by an average of 40 weeks, with a median of 27 and a range of 6 to 173 weeks. Nine of 12 patients had recurrence within 27 weeks (median 6 months) following the onset of pain. Ten of 12 had recurrence within 42 weeks (median 9 months).

Four of six patients who died did so within 1 to 1.5 years after the onset of pain. Five of six died within 2 years following the onset of pain. Of those five, treatment following pain was rendered within 35 weeks.

Pain was described by 10 of 12 patients as "severe" or "excruciating." For two patients, pain was especially severe at night. Pain increased in severity after onset in 11 of 12 patients. Only the patient with laryngeal cancer experienced persistent pain "off and on." Pain had a "shooting," "stabbing," "lightning," or "radiating" character in 8 of 12 patients. "Denture pain" (sore spots) was the only description given of two patients' pain. The exact character of pain was unable to be determined for the remaining two patients.

Trismus was an accompanying symptom in six of eight patients with lancinating pain. Four patients noted regional swelling prior to recurrence, two of whom also had lancinating pain. Two patients complained of headaches, one of whom had a recurrence in the ear canal.

In 6 of 12 patients, pain manifested intraorally and extraorally (Table 4).

Table 3a Location, Symptoms, and Stages of Cancers

Location of primary oral cancer	Symptom/sign	Stage
1. Right retromolar area	Soreness	T3N0M0
2. Right tonsillar pillar	Swelling and pain	T3N1M0
3. Right buccal mucosa	Irritating lesion	RT
4. Right mandibular gingiva	Discomfort followed by pain	TXN0M0
5. Left floor of mouth + pharynx	Discomfort	T1N0M0
6. Right aspect tongue	None—just bulky tumor	T3N0M0
7. Hard palate	Tender lump	T3N0MX
8. Maxilla	Alveolar pain	TXNXMX
9. Base of tongue	Discomfort followed by pain	T2N2bM0
Location of nonoral cancer		
10. Larynx	Difficulty in breathing	T3N0M0
11. Ear canal and parotid	Ear discomfort and pain	n/a
12. Maxillary sinus + left nasal cavity	Nasal obstruction	T1N0M0

Table 3b Primary Tumor by American Joint Committee on Cancer Staging

Primary tumor	No. of patients
RT	1
TX	2
T1	2
T2N2b	1
T3	3
T3N0MX	1
T3N1	1

Table 4 Location of Recurrence and Pain

Location of primary cancer	Recurrence	Pain
1. Right retromolar area	Same as primary	Right maxilla
2. Right tonsillar pillar	Same as primary	Right neck/jaw
3. Right buccal mucosa	Right mandible	Right mandible
4. Right mandibular gingiva	Same as primary	Floor of mouth
5. Floor of mouth	Same as primary	Mandible
6. Right aspect tongue	Same as primary	Left skull
7. Right hard and soft palate	Same as primary	Denture pain
8. Left maxillary alveolus	Left infratemporal fossa	Left cheek + maxilla
9. Base of tongue	Retromolar trigone	Left face, dento-alveolar
10. Larynx	Same as primary	Left mandible
11. Right ear canal + parotid	Same as primary	Right ear
12. Maxillary sinus + left nasal cavity	Same as primary	Left ear

Pain was so severe that 9 of 12 patients were placed on multiple pain medications. The most common were morphine, acetaminophen plus codeine, and acetaminophen plus oxycodone.

Eight of 12 patients had multiple denture adjustments made over several appointments prior to diagnosis of recurrence. The majority had ad-

justments made every 2 to 4 weeks, totaling between 5 and 16 adjustments. These were performed in an attempt to relieve diagnosed denture irritation (Table 5).

In many cases, diagnostic tests gave no indication of recurrence (Table 6).

Table 5 Frequency of Dental Appointments With Pain

Primary cancer	No. of dental appts	No. of weeks	Frequency
1. Right retromolar area	2*	9	4.5
2. Right tonsillar pillar	5	21	4
3. Right buccal mucosa	16	173	10
4. Right mandibular gingiva	12	106	9
5. Left floor of mouth + pharynx	5	42	8
6. Right aspect of tongue	15*	26	2
7. Right hard and soft palate	3	8	3
8. Left maxillary alveolus	12	27	2
9. Base of tongue	2*	17	8
10. Larynx	2	14	7
11. Right ear canal and parotid	8*	24	3
12. Maxillary sinus + left nasal cavity	12	27	2

*Complaints of nondenture pain at appointments.

Table 6 Intervals Between Diagnostic Tests and Confirmed Recurrence

Patient (weeks)	Diagnostic test/ Time 0 (date)	Diagnostic test/ Time 1 (weeks)	Diagnostic test/ Time 2 (weeks)	Recurrence time
1	None			
2	CT- /10.1.93	CT- /18		36
3	None			
4	Pan- /8.26.93	Pan- /53	CT- /54	55
5	Pan- /9.26.91	Pan- /1 day	Pan- /132	151
6	Pan- /8.4.92	Pan- /1	Pan- /25	27
7	None			
8	Pan- /8.4.89	CT+ /8.1.89		2
9	CT+ /6.23.95			
10	None			
11	MRI- /8.20.92	CT- /8	MRI /21	25
12	None			

Time 0 refers to date of first diagnostic procedure.

Time 1, Time 2, and Recurrence time refer to the number of weeks following Time 0.

- or + designates a positive or negative diagnostic finding.

CT = computed tomography; Pan = panendoscopy; MRI = magnetic resonance imaging.

Discussion

Pain in head and neck cancer patients is not rare. Between 40% and 50% of patients experience pain before, during, and after treatment.¹⁴ This suggests that elimination of underlying pathology does not necessarily eliminate pain. The psychologic impact of treatment may account for a heightened perception of pain.¹⁴ Alternatively, posttreatment (especially postsurgical) pain may be attributed to neural damage.¹⁴ Deafferentation has been demonstrated to result in the development of spontaneous neuronal activity and reduced central control mecha-

nisms, ultimately causing neuropathic pain.¹⁴ Radiation has been documented to cause xerostomia and mucositis, and to initiate fibrotic tissue changes.¹⁴ Subsequently, jaw and neck movements may be more painful, and mucosa increasingly susceptible to irritation.

In the present study, however, pain that could reasonably be attributed to dental causes or posttreatment sequelae was excluded. No patients had stage IV primary disease, nor was there an increased incidence of pain associated with any other particular tumor stage. Keefe et al¹⁴ found increased pain with stage III and stage IV tumors,

The cause of posttreatment pain in most patients was typically identified and remedied without difficulty. For example, a denture sore causing pain would be eliminated by adjustment of an overextended flange. Dry socket pain was alleviated by irrigation and an appropriate local dressing.

Assessing postsurgery and/or radiotherapy patients with persistent pain was difficult since xerostomic changes, fibrotic changes, infection, trauma, dental pain (caries, postextraction pain), scar tissue, and possible nerve damage all confound the diagnosis of pain caused by recurrence of cancer. For example, a patient complained of "excruciating toothache-type pain on my lower right" but upon examination no carious lesion, hyperocclusion, periapical involvement, and so forth, was evident. No inflammation, infection, or tissue trauma was observable. Radiotherapy had been the only modality of treatment, so neuropathic pain caused by nerve damage was ruled out. The patient's "toothache pain" nonetheless continued and worsened appointment after appointment.

Another patient complained of "shooting pain from my plate." As the patient was completely edentulous, pain of dental etiology (eg, caries, dry socket syndrome) was ruled out. No scar tissue, trauma, or infection was observable. Radiotherapy had not been used, so irritation as a result of xerostomic changes was ruled out, as was pain secondary to fibrotic jaw changes (which has been reported to be a source of postradiotherapy pain¹⁴). This "shooting pain" from the maxilla ("from the plate" as far as the patient could tell) continued appointment after appointment.

All but one patient was over age 52 and more than half were over 60. The increased age of this group is apparently associated with more sites and severity of posttreatment pain. This may be irrelevant, however, since 72% of new cancer cases occur in those aged 60 and over.¹⁵

Olson and Shedd,¹⁶ in a survey of 51 posttreatment patients, found approximately 35% reporting mild or moderate pain. None reported severe pain. The question remains whether pain in this particular study is simply an artifact of treatment or whether it may in fact be a predictor of recurrent disease. Similar to the study by Keefe et al,¹⁴ pain was reported to originate from locales close to the original site, and more pain sites were reported with time. Pain site and treatment modality failed to influence pain severity or incidence. However, pain was almost always reported as severe rather than moderate and progressively worsened after onset. Pain in 10 of 11 cases began with complaints of denture discomfort, involving different locations at different appointments. Many times, there was no apparent source of

irritation on clinical examination. Additionally, adjustments made by the dentist provided little or no relief. Patients quickly returned repeatedly with similar complaints. This contrasts with the findings of Amagasa et al,¹ who found clinically apparent lesions associated with carcinoma *in situ* of the oral cavity in almost all patients complaining of denture discomfort.

Severe progressive posttreatment pain in association with recurrent tumors has been noted by authors in the past.^{1,3,4,10,14} In a study of pain in 25 head and neck cancer patients, Vecht et al¹³ found that 16 of 19 patients experiencing nociceptive pain had tumor recurrence as the underlying cause. Pain for these particular patients was described as severe in over 80%, continual, and located close to the tumor site. In one third, pain had a "lightning" or "shooting" character.

Pain in the present study similarly had a shooting character in 8 of 10 patients. The median survival time was 2 years following pain. Pain was difficult to control with oral analgesics as reported by Vecht et al.¹³ Trismus was a common complaint in all with lancing pain.

Recurrent tumors may present with symptoms of pain but show no organic evidence of recurrence, as defined by current diagnostic capabilities. Metcetrairut and Brown¹⁰ described a case wherein CT scans, biopsy, and panendoscopy were negative over a 10-month period, only to be positive for tumor recurrence in the twelfth month. Paroxysmal sharp pain continued while these tests remained negative. Shifter and Barrett¹⁷ reported a case of recurrent SCC with no evidence by MRI, CT, or clinical examination until 1 year later, when it was confirmed by biopsy. Sixteen months after the onset of odontogenic pain, CT scans were negative in a patient with a history of prior lymphoma; 3 months later, a second CT scan revealed recurrent tumor.¹⁸

Diagnostic tests were equally ineffective in indicating recurrence in this study. Radiographic evidence of neoplasm was rare. Obviously, small recurrent tumors limited to soft tissue would not be expected to be noticed on a pantomograph. CT and MRI scans were similarly unremarkable.

In the past, complaints of denture pain were considered innocent; the authors were genuinely unaware of any significance. It is obvious that the number of appointments during which pain was complained of does not necessarily reflect a constant span of time. In Table 6, an attempt was made to derive an average frequency of complaints for comparison purposes. The majority of patients returned once every 2 to 4 weeks on average with the chief complaint of oral pain or discomfort.

Conclusions

The results of this study suggest that encounter with a patient with a particular history and profile should alert one to the possibility of a locally recurrent tumor. Such a patient must have a history of cancer, especially of the oral or pharyngeal region.

Within 6 months following treatment, such a patient would in all probability begin complaining of denture irritation in different areas on different visits. Denture adjustments made by the dentist would only provide relief temporarily (possibly only psychologically). The patient would return repeatedly with a similar complaint of denture irritation. In many cases, no apparent area of irritation would be visible clinically, or adjustment would not provide relief at all.

At some point the patient may complain of lancinating pain originating intraorally and often radiating extraorally, commonly to the ipsilateral cheek, temple, neck, scalp, or ear. Pain would almost always correspond to the side of the primary tumor. Pain would be severe, persistent, and intermittent, but not necessarily constant. Pain progressively worsens with time even with administration of pain medications.

On examination, no apparent dental cause for pain can be found. Both clinical and radiologic surveys may be unremarkable. CT and MRI scans are in most cases negative for tumor until 2 to 5 weeks before recurrence is diagnosed. Within 6 months following onset of pain, a recurrent tumor would become evident in the region of the previous primary cancer.

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Resumen

Situaciones de dolor que preceden al cáncer recurrente de cabeza y cuello

Doce pacientes experimentaron la recurrencia de cánceres de cabeza y cuello primarios, durante un período de 7 años precedidos por un dolor orofacial severo. El dolor comenzó dentro de los 6 meses luego del tratamiento en 10 de 12 pacientes y fue progresivo en 11 de 12 pacientes. Seis pacientes murieron debido a la recurrencia, cinco dentro de los 2 años luego del comienzo del dolor. No se detectó una indicación clara de malignidad, a pesar del examen clínico, radiografías simples, imágenes de resonancia magnética, y tomografía computarizada. El dolor fue confundido frecuentemente, con la irritación de la dentadura. No se encontraron áreas de irritación, con mucha frecuencia.

Zusammenfassung

Rezidivierenden Kopf- und Halskarzinomen vorangehender Schmerz

Ueber eine 7-Jahresperiode erlitten 12 Patienten ein Rezidiv eines primären Kopf- und Halskarzinoms, welchem starke orofaziale Schmerzen vorangingen. Die Schmerzen begannen innerhalb von 6 Monaten im Anschluss an die Behandlung und waren bei 11 von 12 Patienten zunehmend. Sechs Patienten starben am Rezidiv, fünf innerhalb von 2 Jahren nach dem Auftreten des Schmerzes. Kein klarer Hinweis auf eine bösartige Erkrankung war offensichtlich trotz klinischer Untersuchung, Flächenröntgenaufnahmen, Kernspintomographie und Computertomographie. Die Schmerzen wurden oft fälschlich für Prothesenreizungen gehalten. Oft war kein gereiztes Areal augenscheinlich.

UMDNJ-New Jersey Dental School Division of Oral Medicine

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