The Role of Chest Computed Tomography in Staging of Oropharyngeal Cancer: A Systematic Review

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ABSTRACT

Background: The prevalence of synchronous or metastatic tumours in patients with head and neck squamous cell carcinoma (HNSCC) ranges from 6-20 % and has implications for prognosis and management of the primary disease. There is no consensus about the role of CT chest prior to definitive treatment patients with HNSCC.

Methods: A systematic review of all CT chest studies in relation to HNSCC was performed, together with a review of our local database.

Results: 24 Studies were identified in addition to our local data. Prevalence of positive CT chest was 7.93 %. Patients were significantly more likely to have a positive CT chest with N2 or N3 neck disease (P=0.0062), stage III or IV disease (P=0.0001) and significantly less likely with tumours of the oral cavity (P=0.0007).

Conclusions: We advocate CT chest as part of the initial investigations for patients with HNSCC.

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the 6th commonest cancer worldwide, and the commonest in the Indian subcontinent. Between 6-20% of patients with newly diagnosed HNSCC will have synchronous or metastatic tumours at initial presentation. These most commonly arise within the head and neck itself, but may also present in the lungs or oesophagus. Furthermore, the presence of distant metastases has implications for the disease free survival of these patients, and may influence their management, particularly when major surgery and reconstruction is planned. The incidence of pulmonary metastases in these patients has traditionally been reported to be 1-2%, but the utilisation of modern screening tool, particularly spiral Computer Tomography (CT) of the chest has suggested that the prevalence of lung metastases is higher.[1]

It is important to identify patients with distant metastases as part of the staging process for newly diagnosed HNSCC. Traditionally the chest was imaged by a plain radiograph but this has low sensitivity, although specificity is high. CT chest

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is currently the gold standard in imaging patients with suspected thoracic malignancy. However, it involves a considerable dose of radiation (on average 8mSv- the equivalent of 400 chest X-rays). Some centres routinely undertake CT chest in all HNSCC patients,[2-10] while others selectively screen those with clinical Stage III or IV disease, or using other clinical criteria such as presence of nodal disease.[1,11-24] In patients with HNSCC, most chest malignancy occurs in the lung apices or mediastinal lymph nodes. As a result, it has been our local policy to perform a limited CT chest from the thoracic inlet to level of pulmonary veins in patients presenting with T1 and T2 tumours (this can be done without moving the patient or giving further contrast). A full CT chest is used in high risk patients, such as those with T3 and T4 disease and in those patients with multiple or large neck node metastases.

The prevalence of positive CT chest in patients with HNSCC in the literature ranges from 1.92 % to 37.5 %. [14,24]

We performed a systematic review of all publications to date, together with a review of our own patient database to identify the prevalence of positive CT chest findings in HNSCC and to provide some recommendations about the appropriateness of CT chest in these patients. We examined subgroups based on factors such as tumour site, TNM classification and disease stage, to determine if any specific risk factors could be identified to select patients who would benefit from CT chest more than others.

METHODS

All publications relating to the use of CT chest in staging HNSCC were identified by searching Medline and Cinahl databases using the terms; oral, pharynx, larynx, squamous cell carcinoma, CT chest. References were hand searched for further relevant publications. Recent conference abstracts were also searched.

All studies were included which contained data on CT chest either alone or in comparison with other imaging modalities (for example plain X-ray or Positron Emission Tomography (PET). All references were searched for data pertaining to prevalence of synchronous bronchogenic primary malignancy or metastatic HNSCC within the chest, sensitivity and specificity of CT chest for malignancy, and tumour data (T classification, N classification, disease stage, primary tumour site and differentiation). Data obtained from abstracts of oral or poster presentations at recent conferences and our local data was included in the analysis to ensure the highest study population was considered.

All studies were graded as level II or level III evidence.

Patient selection criteria were also noted (all patients or selected patients, new or recurrent disease).

Patient data was extracted where possible and grouped by T classification, N classification, disease stage, primary tumour site and differentiation, as per the study description .

Data was analysed with Statsdirect software (© StatsDirect Ltd, Cheshire, UK). Group proportions were assessed using Chi-squared, Fisher's exact and Mantel-Heanszel calculations as appropriate. Study heterogencicity was estimated with Cochrane Q calculation and inter-group bias with Egger's calculation. Differences in data reporting meant that many of the identified publications had to be selectively excluded from subset analysis.

Our own head and neck cancer database was searched for all patients with head and neck (not cutaneous) SCC who had undergone full CT chest during the period 2002-2007. CT chests were reviewed for the presence of malignancy at the time of diagnosis of HNSCC.

Where CT chest reports or imaging was not clear, one author (ET) reviewed the images. Radiology data was further reviewed for the existence of chest imaging within 6 months of diagnosis. Where malignancy was evident within 6 months but not at time of diagnosis the original CT chest was considered to indicate a false negative. For patients with CT chest findings that were non-diagnostic further investigations such as fine needle biopsy, PET-CT or interval scans were considered. We do not routinely advise invasive investigations for suspicious findings but rather repeat suspicious chest imaging again at 1-3 months, as a result of which we did not determine any CT chest to be false positive. The primary tumour site, T classification, N classification, disease stage and tumour differentiation were all established, where possible from clinical and pathology records. This data was included in the systematic review.

RESULTS

Review of local database:

Between July 2002 and March 2007, we identified 195 patients with newly diagnosed head and neck SCC who had undergone partial (n=118) or full (n=77) CT chest as part of their staging investigations.

Of those patients who underwent partial CT chest, 5 (4%) had positive findings for chest malignancy, while 10 (13%) had a positive CT chest following a full CT chest. Patients who underwent partial CT chest were significantly less likely to have a positive CT chest than those who underwent a full CT chest (OR 0.2982, 95% CI 0.0893 to 0.9093, P=0.0307). Interestingly, in 8 out of the 10 patients who had positive findings on full chest scans, the abnormality was within the upper thorax, which would have been identified by partial CT scanning.

Some patients underwent the incorrect scanning protocol and when full and partial scan were compared taking in to account tumour size (T1 or T2 compared to T3 or T4), the type of scan did not significantly affect the likelihood of a positive result (OR 1.3518 95% CI 0.3956 to 4.6191).

Systematic review:

Twenty-two published studies were identified, together with two abstracts from conferences in addition to the data from our own database. There were 14 prospective and 11 (including our own) retrospective studies.

CT chest was performed in all patients presenting with head and neck squamous cell carcinoma in 16 papers, while 9 groups used CT chest selectively for high risk groups identified according to various criteria, including tumour size, neck node status, disease stage, and whether it was primary or recurrent disease.

Overall the data represented some 4062 patients with 322 true positive CT chest. Analysing studies which reported outcomes of all scans including false negative and false positive staging CT chest scans reveals the sensitivity of CT chest for identifying synchronous tumours or metastasis to be 84.62% and the specificity to be 93.50%.

The pooled point prevalence of positive CT chest in patients with HNSCC is 7.93 % (95% CI 7.10 to 8.76). There was significant heterogenicity of study results (Cochran Q 213.04 (P<0.0001)) and therefore any assumptions based on pooled data must be interpreted with caution.

Figure 1 demonstrates the published prevalence of positive CT chest findings with studies grouped according to the author's use of patients with new,

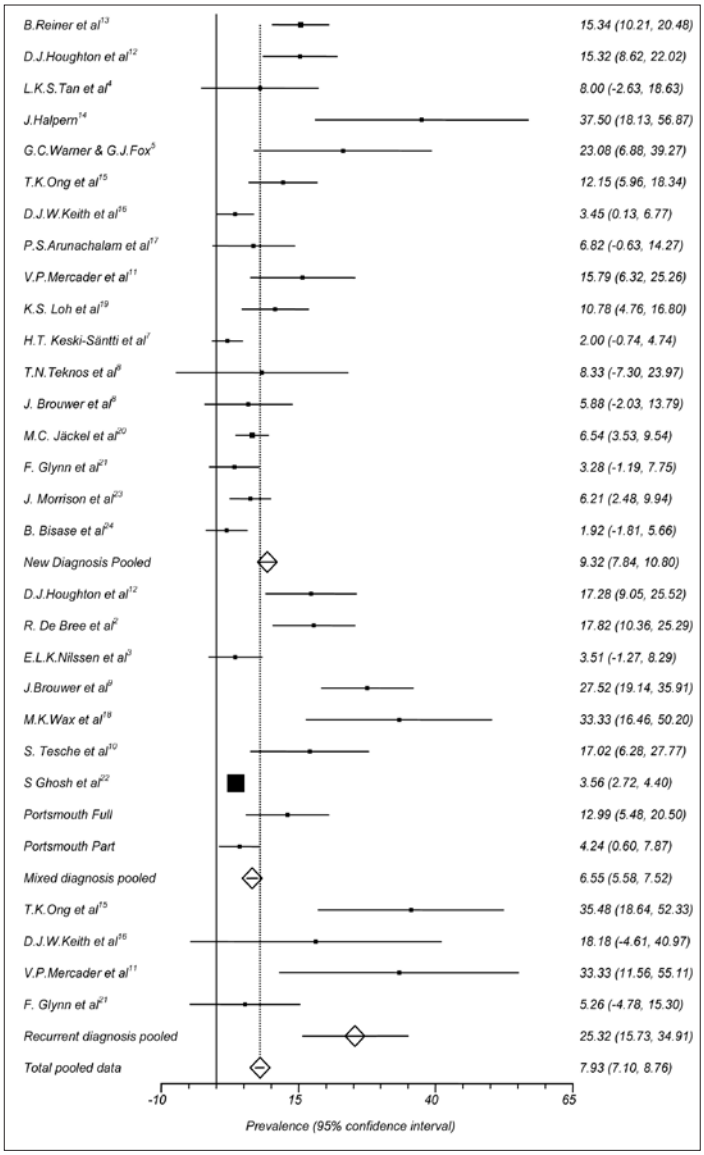

Figure 1. Forest plot of prevalence of positive CT chest findings. Studies grouped according to existence of previous HNSCC diagnosis.

recurrent or mixed HNSCC.

There was a significantly higher point prevalence of positive CT chest in studies examining patients diagnosed with a recurrent HNSCC compared to those with a first diagnosis of HNSCC or mixed groups of patients (Chi Square = 43.1118, P < 0.0001) (Table 1). In studies which included identifiable data for new and recurrent diagnosis patient groups there was no evidence of study heterogenicity (Cochran Q 1.6726, P = 0.64) or group bias (Egger 1.6370, P = 0.0918)

There was a significantly higher point prevalence of positive CT chest in studies which undertook CT chest in selected patients and not all patients presenting with new HNSCC (13.89% compared to 7.17%). (Table 1)

The style and detail of the reported data varied greatly and therefore only selected data could be included in further sub-group analysis. Results of the different subgroups analyses are shown in Table 2.

Table 1 Subgroup analysis based on patient selection criteria (* = p<0.05)

	Prevalence	**Odds Ratio**	**95% CI**
Diagnostic history			
First diagnosis	9.32%		
Mixed	6.55%	0.6420	**0.5072 to 0.8137***
Recurrance	25.32%	3.2440	**1.7944 to 5.6471***
Selection			
All patients	7.17%		
High risk patients	13.89%	2.0905	**1.5686 to 2.7622***

PRIMARY TUMOUR SIZE (T-STAGE)

There were 7 studies (427 patients) that included data on the T-stage. A total of 52 (12%) patients had positive CT chest findings. There were significant differences in the proportion of patients with positive CT chest with different T classifications (Chi square 15.98, P=0.0011), principally due to an increased prevalence in patients with T3 tumours (Table 2). There was no evidence of group bias (Egger -1.0069, P=0.37).

The prevalence of positive CT chest in patients with T1 and T2 tumours grouped together was not significantly lower than that for patients with T3 and T4 tumours grouped. (prevalence 9.52% compared to 12.50%, OR = 1.6096, 95% CI = 0.7351 to 3.3247).

NECK LYMPH NODES (N-CLASSIFICATION)

There were 7 studies (440 patients) that included data on the disease N-classification. A total of 52 (11.82%) patients had positive CT chest findings. There was a significant difference in the proportion of patients with positive CT chest with different N classifications (Chi-square = 8.1000, P = 0.044), the prevalence increasing with increasing N classification (Table 2). There was no evidence of group bias (Egger 2.2364, P=0.07).

Patients with N0 or N1 neck node classification were significantly less likely than those with N2 or N3 necks to have a positive CT Chest (prevalence 7.42% compared to 16.54%, OR = 0.4431, 95% CI = 0.2237 to 0.8775).

DISEASE STAGE

There were 13 studies (1359 patients) that included data on disease stage. A total of 110 (8.09%) patients had positive CT chest. There was no significant difference in the proportion of patients with positive CT chest based on the individual disease stage (Chi-square = 3.8305, P = 0.28) (Table 2). There was no evidence of group bias (Egger -1.0812, P=0.36).

When Patients with Stage I or II disease were grouped, the prevalence of positive CT chest was significantly lower than those with disease stage III or IV grouped (Prevalence 3.47% compared to 10.47%, OR = 0.4053, 95% CI = 0.12264 to 0.7254).

SITE OF PRIMARY DISEASE

Eleven studies (1149 patients) included data on the site of primary disease. A total of 110 (9.57%) patients had

positive CT chest findings. Significant differences in the prevalence of positive CT chest findings existed according to site (Chi-square = 10.8367, P = 0.0126) (Table 2).

A primary tumour in the oral cavity was significantly less likely to be associated with a positive CT chest than all other sites grouped (prevalence 5.30% compared to 11.67%, OR 0.4233, 95% CI 0.2416 to 0.7104, P = 0.0007).

Table 2. Subgroup analysis of grouped data. (* = p<0.05)

	Prevalence	Odds Ratio	95% CI
T classification			
T1	4.17%		
T2	12.50%	3.2857	0.4640 to 77.6528
T3	27.66%	8.7941	**1.3593 to 196.2583***
T4	6.87%	2.3590	0.3921 to 52.0213
N Classification			
N0	8.39%		
N1	8.22%	0.9782	0.3296 to 2.6562
N2	11.84%	1.4673	0.5744 to 3.6181
N3	29.41%	4.5513	**1.2519 to 14.7342***
Stage			
Stage I	2.88%		
Stage II	4.35%	1.5303	0.3919 to 7.4213
Stage III	5.58%	1.9901	0.5832 to 8.9525
Stage IV	8.50%	3.1271	**1.0617 to 12.8928***
Site			
Oral Cavity	5.30%		
Larynx	12.13%	3.1706	**1.29.4 to 8.7429***
Pharynx	11.27%	3.5778	**1.5662 to 9.3991***
Unknown	15.38%	5.4444	0.6614 to 29.6496
Differentiation			
Well	9.09%		
Moderate	14.58%	1.7032	0.2536 to 39.9095
Poorly	13.79%	1.6000	0.1730 to 43.3348

TUMOUR CELL DIFFERENTIATION

Three studies (238 patients) included data on the degree of primary tumour differentiation. A total of 30 (12.6%) patients had positive CT chest findings. There was no significant difference between degree of tumour differentiation and existence of positive CT chest findings (Chi-square = 0.2487, P = 0.8831) (Table 2)

DISCUSSION

The presence of a synchronous bronchogenic tumour or chest metastases when a patient presents with HNSCC has implications for the prognosis of the patient, and may have a major impact on their management.

Whilst in some cases the chest lesion may be amenable to resection or chemo-radiotherapy and therefore the treatment of the primary HNSCC unaffected, in other cases the patient will be deemed to have incurable disease and extensive resection or aggressive chemo-radiotherapy of the primary HNSCC may be inappropriate. Whilst there are questions as to the survival benefit of population chest malignancy screening with either CXR or CT chest the impact of a positive investigation on the management of HNSCC makes screening for chest malignancy in this population group important. Mazer et al,[25] Finlay et al[26] and Young et al[27] have all demonstrated a clear survival benefit in patients with HNSCC with lung metastases who underwent surgical resection of their lung metastases. Screening of the chest for synchronous or metastatic HNSCC is therefore clearly indicated.

The Scottish Intercollegiate Guidelines Network (SIGN) have advocated that all patients with HNSCC should undergo CT chest as part of their staging investigations, despite their being little evidence to support the benefit to this move.[28] The National Institute of Clinical Excellence (NICE) document 'Improving Outcomes in Head and Neck Cancer' states that "all patients with upper aerodigestive tract (UAT) cancers should have chest X-rays. Other forms of imaging are necessary to assess the stage and spread of the tumour, and specialist ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) should be available. Positron emission tomography (PET) imaging should be used, if available, when it is important to differentiate between benign and malignant lung nodules. It is anticipated that the role of PET will increase over the course of the next decade".[29]

Plain chest radiography, usually in the form of a plain postero-anterior chest film has traditionally been used for both population screening for primary chest malignancy and screening for chest malignancy in the patients with other primary tumours.

Studies where CXR results were compared to those of CT chest demonstrate a pooled sensitivity of CXR of 42.68% with a specificity of 98.47%.[2,4,5,12-16,18] CXR is therefore only half as sensitive as CT chest, although its specificity is comparable.

The sensitivity and specificity of Chest CT currently make it the gold standard in screening for chest malignancy although its use for population screening for chest malignancy is limited by the lack of evidence of a survival benefit in unselected population groups.[30]

The sensitivity of PET –CT is high (96-100%), making it much more sensitive than CXR and slightly more so than CT chest in identifying chest malignancy, but its specificity (77.8%) is poor compared to either modality.[8,18,31,32] When combined with its high cost and limited availability, particularly in Europe and Asia, these findings do not support its use for routine staging for chest malignancy in patients with HNSCC at present.

In addition to the advantages of detecting malignancy not evident on a plain CXR, which may change both patient management and prognosis, there are disadvantages of CT chest which must be considered.[1] These include additional radiation and the risk of false positive results, necessitating other investigations whilst increasing patient anxiety still further.[16] Ideally these risks could be minimized and the benefit of CT chest maximized by identifying those patients who are most at risk of malignant lung pathology, but as yet there is no consensus on the best approach to identifying higher risk patients.[32]

The reported point prevalence of synchronous or metastatic chest malignancy, in patients with head and neck SCC, varied from 1.90% to 37.50% with significantly higher prevalence in studies which examined patients with recurrent disease compared to new (first diagnosis) patients and also in centres which used CT chest selectively. There is an element of selection bias in all studies as they report on the basis of CT chest undertaken and reported and not on an intention to treat basis (including all patients with HNSCC).

T Stage alone is not a reliable indicator of likelihood of identifying chest malignancy. Whilst there is an increasing prevalence of chest malignancy with increasing T classification from T1 to T3 tumours, those with T4 tumours have a lower prevalence. T classification does not simply reflect tumour size. T4 tumours are defined as invading local structures, for example the mandible or maxilla in oral cancer, irrespective of size. The lower prevalence in T4 tumours may indicate over-staging of tumours due to their proximity to other structures or the different biological behaviour of different tumours. The ability of small tumours to metastasize, whilst others will become locally very advanced before metastasizing is recognised.

Patient who have N2 or N3 neck disease are more likely to have synchronous or metastatic chest malignancy as are those with stage III or stage IV disease, and these indices could be used to select high risk patients. However it is not clear in the published studies whether the authors were using initial clinical classifications of neck lymph node disease or pathological staging, which would result in greater disease staging, after investigations are completed.

Unfortunately there was insufficient data in the studies analysed to include pathological parameters such as extra-capsular spread (ECS), and position of the metastatic nodes. However, it is generally agreed that these variables as well as the number of nodes involved are associated with increased risk, and most authorities would cite three or more nodes as having particularly poor prognosis.[33-36]

Whichever selection criteria were used, when study data was pooled the point prevalence of positive CT chest was at least 2.88% for all sub-groups (stage I tumours) (table 1, 2). This is higher than the prevalence of chest malignancy in studies on the use of CT chest in screening high risk patients for chest malignancy (0.3 to 2.3%) and for breast malignancy in screened patients (0.60%).[30,37] And whilst the current cost:benefit or survival benefit arguments have not favoured the development of a population based chest malignancy screening program, one does exist in most developed countries for breast malignancy.

CONCLUSIONS

Improvements in treatment of HNSCC have resulted in better loco-regional control, however the mortality rates have barely improved over the last 30 years, and most would attribute this to the development of distant metastases.[33-36,38] Furthermore, HNSCC cells can be found in the bone marrow in these patients, although the significance of this finding is unclear.[39] The early detection of distant metastases therefore is important because of its possible effects on the treatment planning of the patient. Major ablative and reconstructive surgery should only be considered where there is a reasonable prospect of effecting a cure and whilst the presence of distant metastases would not in itself contra-indicate surgery, treatment of the distant site would need to be considered as well.[12,13] This may take to form of thoracic surgery or chemo-radiotherapy.

CT chest is currently the gold standard investigation for primary and metastatic chest malignancy.

Because of the difficulties in accurately identifying patients at higher risk of having synchronous or metastatic chest malignancy and the survival and cost benefits in identifying the presence of synchronous or metastatic chest malignancy, we would advocate the use of CT chest in all patients presenting with HNSCC.

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