

Tumour volume measurement in head and neck cancer

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Abstract

Tumour volume is a significant prognostic factor in the treatment of malignant head and neck tumours. Studies of laryngeal and pharyngeal tumours have shown tumour volume to be an important predictor for tumour recurrence. Some studies (for instance nasopharyngeal carcinoma) have shown through multivariate modelling that tumour volume is a dominant covariate that overwhelms T stage, N stage and stage group. The results of these studies have prompted several investigators to suggest the inclusion of tumour volume as an additional prognostic factor in future revisions of the TNM staging system. This paper briefly reviews the TNM system as a staging tool, the measurement of tumour volume and how tumour volume could possibly be incorporated in the system or used as an additional prognostic factor.

Keywords: *Tumour volume measurement; nasopharyngeal carcinoma; laryngeal carcinoma; TNM staging system.*

Introduction

There is an increasing interest in the relationship between tumour volume and treatment outcome over the last 10–15 years. With the continued improvement in segmentation algorithms and advances in computer technology it now appears possible to measure the volume of malignant tissues from computed tomography (CT) and magnetic resonance (MR) images.

Tumour volume is now known to be a significant prognostic factor in the treatment of malignant tumours^[1–6]. Investigators have suggested the importance of incorporating tumour volume into the TNM staging system. However, if tumour volume is to be used as an independent prognostic factor, it is imperative that the methods for volume measurement be standardised, robust and reliable. Unfortunately, to date, there are no simple or user-friendly systems to achieve the desired level of accuracy and reproducibility in results for routine clinical practice.

Staging and the TNM Classification System

The TNM System for the classification of malignant tumours was developed by Pierre Denoix between 1943 and 1952^[7–10]. The objectives of the TNM System are to

(1) aid the clinician in the planning of treatment, (2) give some indication of prognosis, (3) assist in the evaluation of the results of treatment, (4) facilitate the exchange of information, and (5) contribute to continuing investigations of human malignancies^[11]. Hence, an understanding of the natural history of a malignancy (which guides the selection of an appropriate treatment option) and the comparison of treatment outcome are central to the aims of the TNM System. The measurement of tumour volume may provide a further tool to achieving these purposes.

The TNM System was originally constructed to assess only three basic indicators of anatomic spread, that is, the local tumour extent (T), locoregional nodal spread (N) and distant metastasis (M). This system, like any other system, is not perfect and over the years, non-anatomic factors were included to further refine prognostic accuracy^[12,13]. For instance, in the staging of thyroid cancers, additional prognostic factors include sex, age and histology of the lesion. Similarly in the staging of liver cancer, the alpha-fetoprotein, total bilirubin and alkaline phosphatase levels are taken into consideration. In recent years, efforts have been directed at elucidating the relationship between the TNM system and tumour volume in stratifying patients into prognostic groups. Such stratification has a direct relationship with the objectives of the TNM system.

The TNM System recognises the importance of tumour volume. Currently, about half of the malignant head and neck tumour subsites are T-classified by a single dimensional measurement which acts as a surrogate measurement for tumour volume. Tongue, oropharyngeal and hypopharyngeal carcinomas, for instance, are classified as follows: T1 tumours, measures less than 2 cm; T2 tumours, between 2 cm and 4 cm; and T3 tumours measure more than 4 cm in diameter.

However, Sorensen *et al.* have demonstrated that the differences in volumes derived from diameter measurement and the computer-assisted perimeter method was large enough to have an impact in gauging the response of treatment^[14]. Furthermore, staging based on subjective and single dimensional measurement is often questionable. For instance, superficial spreading carcinomas frequently exceed 4 cm in diameter without deep penetration. These tumours are classified as T3 lesions but have very low volumes. It is now known that the depth of the tumour in tongue carcinoma is a good predictor of lymph node metastases.

Tumour volume and treatment outcome

Various reports in the literature have recognised a positive correlation between tumour volume and prognosis for various head and neck subsites^[16–18]. Several authors have noted that tumour volume is a better predictor of treatment outcome compared with the TNM System^[3–6]. The basis for this observation is easy to understand. T-classification remains dependent upon subjective and single dimensional criteria which may fail to define the true three-dimensional tumour volume. Studies have demonstrated a tremendous variation in tumour volume within any of the T-classification groups^[15,19].

The probability of cure depends on a number of factors, including the initial number of tumour clonogens. It is also known that the number of tumour clonogens increase linearly with tumour volume. Hence tumour volume can be a useful predictor (prognostic factor) of local treatment outcome^[18]. If tumour prognosis depends on the number of tumour clonogens to be sterilised, it can be seen that a single dimensional measurement appears inadequate for prognostication. Furthermore, for some tumours such as laryngeal and nasopharyngeal carcinoma, T-classification is determined by only anatomical structure involvement, irrespective of tumour size inferred by anatomical extent or measurements. Hence a small tumour affecting a critical area may have a higher T-classification compared to a large tumour confined to a defined anatomic site.

Tumour volume measurement issues

Even to date, technical considerations have prevented tumour volume measurements from being routinely used in a clinical setting. The measurement of tumour volume has always been tedious. It involves tracing the tumour outline and the volume is derived by the summation of area technique. Whether this process is done by a radiologist or by a technician, there is always an important element of subjectivity that results in both intra- and inter-operator performance^[20–22]. To overcome this problem, several investigators have developed semi-automated or automated systems to reduce inter-operator as well as intra-operator variability^[23–25]. Errors encountered by computer-based techniques are thus likely to be classified as systematic errors and not as a result of, for example, the experience of the operator.

Investigations highlighting the relationship between tumour volume and treatment outcome bring into question the validity of the tumour volume measurement methodology employed by various investigators. For instance, in the landmark paper by Chua *et al.*^[3], there was no mention of validation of the tumour volume measurement methodology. Similarly, in a subsequent report by Willner *et al.*^[4], there was also no validation study on the volume measurement technique used in their study. In addition, volume measurements were performed on digitised hard copies and the reliability of this technology is uncertain. Sze *et al.*^[6], in contrast, used a more elaborate method. The tumour outline was first drawn by a diagnostic radiologist on MR images. These images were then transcribed by the radiation oncologist to the CT planning system where tumour volume was calculated. The inter-operator variance or inter-observer variability of this method also remains unknown. The need for validated tools and a consensus on measurement criteria appear clear under such circumstances.

Computer-based tumour volume segmentation

The development of segmentation algorithms is central to tumour volume measurement. Generic segmentation algorithms were originally developed as image processing tools in a variety of engineering applications. In recent years some of these algorithms were modified and adapted for possible medical imaging purposes. Newer algorithms are now being developed and tested specifically for medical imaging needs. They include: (1) deformable models (active contour and level set); (2) machine learning-based approach (support vector machine) with shape prior; (3) atlas-based segmentation; and (4) spectral clustering and normalised cut.

Before any of the above imaging-based tumour volume measurement methods can gain acceptance in clinical practice, information on inter-observer and intra-observer

variability in tumour volume estimation is necessary. For instance, Hermans *et al.*^[26] showed that in the measurement of laryngeal tumours based on CT images, the most important component of total variability was inter-observer variability (89.3%) while intra-observer variability accounted for only 6.4%. These findings were attributed to the experience of the observer in head and neck radiology and the complex pattern of tumour spread.

The study by Hermans *et al.*^[26] highlights the importance of developing tumour volume measurement methods that are not critically dependent on operator ability. One of the most desirable features of computer-based automated or semi-automated tumour segmentation is the minimisation of inter- and intra-observer variability.

TNM System and tumour volume

Assuming we already have validated and robust tools for measuring tumour volume, it is interesting to speculate how tumour volume might be introduced into the TNM system. One possible way is to replace is to directly replace tumours that are currently staged with single dimensional measurements with tumour volume. For tumours currently staged by only anatomical extent, further work will be required to determine the relationship between tumour volume and T classification.

Conclusion

In conclusion, investigations in recent years have identified an important relationship between tumour volume and treatment outcome. The initial challenge is to develop validated measuring tools that can be used in a clinical setting. The next challenge is to determine the relationship between T-classification and tumour volume derived from the validated tools.

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