3D model-based documentation with the Tumor Therapy Manager (TTM) improves TNM staging of head and neck tumor patients

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Abstract

Purpose Many treatment approaches are available for head and neck cancer (HNC), leading to challenges for a multidisciplinary medical team in matching each patient with an appropriate regimen. In this effort, primary diagnostics and its reliable documentation are indispensable. A three-dimensional (3D) documentation system was developed and tested to determine its influence on interpretation of these data, especially for TNM classification.

Methods A total of 42 HNC patient data sets were available, including primary diagnostics such as panendoscopy, performed and evaluated by an experienced head and neck surgeon. In addition to the conventional panendoscopy form and report, a 3D representation was generated with the “Tumor Therapy Manager” (TTM) software. These cases were randomly re-evaluated by 11 experienced otolaryngologists from five hospitals, half with and half without the TTM data. The accuracy of tumor staging was assessed by pre-post comparison of the TNM classification.

Results TNM staging showed no significant differences in tumor classification (T) with and without 3D from TTM. However, there was a significant decrease in standard deviation from 0.86 to 0.63 via TTM \((p = 0.027)\). In nodal staging without TTM, the lymph nodes (N) were significantly underestimated with \(0.39\pm0.79\) classes compared with \(0.07\pm0.69\) with TTM \((p = 0.002)\). Likewise, the standard deviation was reduced from 0.79 to 0.69 \((p = 0.032)\). There was no influence of TTM results on the evaluation of distant metastases (M).

Conclusion TNM staging was more reproducible and nodal staging more accurate when 3D documentation of HNC primary data was available to experienced otolaryngologists. The more precise assessment of the tumor classification with TTM should provide improved decision-making concerning therapy, especially within the interdisciplinary tumor board.

Keywords Tumor Therapy Manager · Head and neck cancer · Documentation · Three-dimensional · Patient data · Reproducibility · Panendoscopy · TNM staging

Introduction

The worldwide incidence of head and neck cancer (HNC) in 2008 has been rated 634,760 by the World Health Organization (WHO) and hence represents 5.1% of all cancer diseases [1]. In the mentioned year, there were 47,560 cases counted in the USA [2] and 17,130 in Germany [3]. Current estimations even assume an incidence of 53,640 for 2013 in the USA [4]. While the number of head and neck malignancies attributable to the primarily dominant risk factors alcohol
and smoking decreased as a result of lowered consumption, the human papillomavirus (HPV)-associated entities came to the fore and are supposed to cause the rising incidence in particular of oropharyngeal head and neck squamous cell carcinoma [5,6].

The epidemiological changes and the enormous developments in diagnostics and therapy of HNC in the recent years have led to a more complex treatment management. Medical imaging with sonography, computer tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) has been broadened by higher resolutions and hybrid systems like PET-MRI. On the other side, there was a diversification of treatment approaches such as organ-preserving surgery, combined radiochemotherapy and targeted therapies with biologicals or intensity-modulated radiation therapy (IMRT) [6–8]. This requires the inclusion of all available information allowing for an intensified decision-making process taking into consideration not only primary staging data such as radiological images, pathological and molecular findings but also the clinical and haptic impression. Today, various specialists are involved in the treatment of HNC besides otolaryngologists: radiologists, radiotherapists, oncologists, pathologists and maxillofacial surgeons. Hence, according to several authors, the diagnostic findings and the therapy options for the individual patient should be discussed, agreed and scheduled within multidisciplinary head and neck oncology boards [9,10]. In addition, Simo et al. claim an integrated media presentation in these conferences [11].

With the “Tumor Therapy Manager” (TTM) developed by our group, a three-dimensional (3D)-based documentation system is available, which integrates the above-mentioned data of the tumor and the patient [12,13]. This computer program is capable to manage segmented CT scans, anatomic 3D reconstructions, endoscopic photographs or sketches with annotations and also allows spatial distance measuring and 3D volumetry. We could demonstrate that the TTM is operational in the daily routine [14]. However, no investigation so far addressed the question whether the integrated presentation of information using the TTM indeed increases the reliability of documentation and leads to a better reproducibility of the tumor evaluation. In the presented study, these aspects were investigated with focus on reproducibility of staging by means of the TNM classification. This classification system describes the spread of the primary tumor (T), locoregionary lymph node metastases (N) and distant metastases (M). Since these factors are very important regarding treatment options and in particular of prognostic relevance, the TNM classification is the most common tumor classification, referring also to HNC [15]. The TNM system is used for decision-making regarding the treatment according to the national therapy guidelines.

Methods

To investigate the accuracy of tumor staging, i.e. the validity and the reliability of the conventional and our three-dimensional documentation of HNC, a prospective randomized controlled multicenter study with re-evaluation of the TNM status was done. We involved experts in the field of head and neck oncology. The trial was based on real data sets of HNC patients which was judged to be the most appropriate way to detect a potential benefit provided by the TTM.

Therefore, the investigation was conducted in two phases. First, individual HNC patient data were gathered, which served as a basis for the actual study, i.e. the re-evaluation by otolaryngologists.

Data acquisition

In the period from 05/2011 to 09/2012, the primary staging data of 42 HNC patients at the Department of Otolaryngology of the University Hospital Leipzig were prospectively acquired considering the following inclusion criteria: first panendoscopy related to the first diagnosis of HNC, head and neck CT scan of appropriate quality in regard to the distribution of the contrast agent as well as the slice thickness ≤3 mm, and an advanced tumor stage (UICC III or IV) to allow further evaluation of the N classification. The sample can be considered representative for mean age, sex ratio and distribution in tumor localisation (Table 1).

The CT scans have been segmented by the first author, who was at this time in the 10th term of medical studies and advised by an oncological trained head and neck

<table>
<thead>
<tr>
<th>Mean age (±SD)</th>
<th>59.8 ± 11.0</th>
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<tbody>
<tr>
<td>Sex ratio (m/f)</td>
<td>38/4</td>
</tr>
<tr>
<td>Localisation</td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>4</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>16</td>
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<tr>
<td>Hypopharynx</td>
<td>13</td>
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<tr>
<td>Larynx</td>
<td>9</td>
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<td>UICC classification</td>
<td></td>
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<tr>
<td>0</td>
<td>–</td>
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<tr>
<td>I</td>
<td>–</td>
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<td>II</td>
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<tr>
<td>III</td>
<td>3</td>
</tr>
<tr>
<td>IVA</td>
<td>30</td>
</tr>
<tr>
<td>IVB</td>
<td>7</td>
</tr>
<tr>
<td>IVC</td>
<td>2</td>
</tr>
</tbody>
</table>

SD standard deviation, m male, f female

Table 1: Mean age, sex ratio, tumor localisation and UICC classification of the 42 HNC patients
radiologist. The segmentation process was performed with the software “NeckSegmenter” [16], and then, 3D models were generated from the segmentation data in the TTM prior to the panendoscopy (Fig. 1). This took approximately 90 min depending on the number of slices and the quality of the CT scan (e.g. metal artefacts by dentures in the oropharyngeal region) as well as level of detail in 3D structures. The NeckSegmenter provides manual, semi-automatic and fully automatic algorithms. The tumor itself is segmented manually slice by slice due to vague delineation, likewise the lymph nodes. Anatomic landmarks such as vessels, muscles and bones are detected and segmented with semi-automatic algorithms based on regional growing, interpolation between regions of interest (ROI) in distant slices and thresholds of Hounsfield units. For the thyroid cartilage, a predefined model is processed to landmarks in the CT scan.

To avoid interobserver variability in the data sets used for re-evaluation, a single proven head and neck surgeon solely performed the panendoscopies and primary documentation. Each data set was pseudonymised and includes a standardised patient’s chart (anamnesis, ENT examination findings, conventional and new 3D panendoscopy form (Fig. 2), panendoscopy report, endoscopic photographs, radiological findings, internistic status) plus the CT data in Digital Imaging and Communications in Medicine (DICOM) format and the 3D documentation in TTM (Fig. 3).
Fig. 3 Screenshots of the documentation available in the TTM. a CT with highlighted structures (yellow: tumor, red: arteries, blue: veins), b tumor with measurement of volume and distance to the artery as relevant structure at risk, c panendoscopic photographs with annotations (the inserted pictogram of the instrument marks the point where the biopsy was taken for histopathological diagnostic), d pictograms of tumor spread

Setting for re-evaluation

We could engage 11 experienced otolaryngologists (see acknowledgements) from five hospitals in Cottbus, Erfurt, Leipzig, Potsdam and Riesa (Germany) to re-evaluate the patient data.

A detailed test protocol was set up to check for reproducibility of the tumor classification. The 42 patients were randomized to 10 blocks each of 5. Thus, eight patients were allocated twice. One physician examined two of these blocks, the first one with and the second block without the TTM data. The next physician received the same patients in identical order, but first without and then with the TTM data to prevent a bias through conditioning. Hence, every patient was randomly assigned to the re-evaluating otolaryngologists and re-evaluated in each of both ways, and ten patients were re-evaluated multiple times.

The patient’s chart as well as the head and neck CT scan was available in both settings. In the TTM cases, the conventional panendoscopy form was replaced with the 3D form and in addition the physicians had access to the 3D documentation in TTM. The assumed TNM classification was recorded on a test sheet. There was no time limit given for the re-evaluations.

Assessment of classification accuracy

For comparison of the results in both groups, the difference between re-evaluation and primary diagnosis was expressed in classes for each state T, N and M. Since the TNM classification is defined by ordinal parameters, specific intervals were determined. More precisely, the difference between two adjacent main classes (T0–4; N0–3; M0–1) was defined as one (1). The interval between the subclasses T4a and T4b was set to one half (1/2) and within N2a–N2c to one-third (1/3). If for example a re-evaluator stated the classification of locoregionary lymph nodes N2b instead of the primarily diagnosed N1, the N status was judged to be overvalued +1/3 classes (Fig. 4). Undefined stages (Tx, Nx, Mx) were not taken into account.
In the re-evaluation without TTM, the lymph nodes (N) were significantly underestimated with $-0.39 \pm 0.79$ classes compared with TTM with $0.07 \pm 0.69$ ($p = 0.002$). Likewise, the standard deviation was reduced from 0.79 to 0.69 classes ($p = 0.032$).

Distant metastases were classified with a deviation of $0.02 \pm 0.15$ classes in the TTM group and $0.05 \pm 0.21$ without 3D documentation ($p = 0.549$). Since the 3D model in the TTM is based on head and neck CT scans and does not represent the total $M$ state, information on this was taken from the patient record in both groups, which explains the missing influence on the corresponding re-evaluation results.

### Discussion

The results show a clear advance regarding the reproducibility of the TNM classification by the TTM documentation system.

Unfortunately, there are currently no further comparative studies that address the reproducibility of HNC data in repeated assessments based on recorded data, but our results demonstrate that the use of superior 3D visualisation in clinical decision-making should be of high value. Reasons for this are attributable to numerous clinically relevant aspects. It is not only the lowered variance in TNM classification, and hence, a better reproducibility of initial findings in a second look but rather the transferability of results obtained within the same and also external departments and e.g. in clinical trials.

The most relevant aspect addresses the definition of the appropriate therapy of the individual patients due to technical estimates of resectability specific tumor extent. An underestimation in particular of lymph node metastases can lead to inappropriate treatment, for instance avoidance of the required neck dissection or adjuvant irradiation or chemotherapy. This was observed in our trial by re-evaluation of the $N$ status without TTM, which showed a systematic underestimation (Fig. 6). Furthermore, an overestimation of $T$, $N$ and $M$ can also harm the patient due to inappropriately intensified treatment regarding irradiation, radiochemotherapy or extended surgery. Inoperability of the primary tumor (T4b) was falsely stated in re-evaluation with and without TTM in 2 and 5 of 55 cases, respectively. In other words, an inappropriate high rate (9.1%) in omission of a surgical treatment option for the primary tumor in these cases can be reduced to 3.6% by integration of 3D visualisation and documentation in the TTM. Since multimodal treatment including surgery leads to improved outcome [17], we have good reasons for integration of 3D visualisation into clinical routine.

However, these advantages are naturally based on certain efforts that have to be accomplished. First, there is

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>With TTM</th>
<th>Without TTM</th>
<th>$p$</th>
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<tbody>
<tr>
<td>T</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mean</td>
<td>$-0.04$</td>
<td>$-0.05$</td>
<td>0.950 (Student’s $t$ test)</td>
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<tr>
<td>• SD</td>
<td>0.63</td>
<td>0.86</td>
<td>0.027 (Levene’s test)</td>
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<tr>
<td>• n</td>
<td>55</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mean</td>
<td>0.07</td>
<td>$-0.39$</td>
<td>0.002 (Student’s $t$ test)</td>
</tr>
<tr>
<td>• SD</td>
<td>0.69</td>
<td>0.79</td>
<td>0.032 (Levene’s test)</td>
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<tr>
<td>• n</td>
<td>55</td>
<td>53</td>
<td></td>
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<tr>
<td>M</td>
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</tr>
<tr>
<td>• Mean</td>
<td>0.02</td>
<td>0.05</td>
<td>0.549 (Student’s $t$ test)</td>
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<tr>
<td>• SD</td>
<td>0.15</td>
<td>0.21</td>
<td>0.228 (Levene’s test)</td>
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<tr>
<td>• n</td>
<td>44</td>
<td>43</td>
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the CT segmentation and the generation of the 3D model, which takes about 90 min and has to be prepared prior to the panendoscopy. The actual documentation process is performed right after the endoscopic examination and lasts further 10 min longer than conventional paper-based documentation [14]. To minimise the time exposure, it is necessary to automate the segmentation process as much as possible. Lymph nodes were segmented manually within the here presented investigation, but meanwhile, a semi-automatic algorithm for lymph node segmentation is implemented in the NeckSegmenter [18] reducing the additional time effort.

Moreover, the documentation system should be implemented in the hospital information system but also into the picture archiving and communication system to avoid recurrent manual user inputs, data disruption and mistaken identities. Bohn et al. described an integrated IT platform, which addresses these problems [19] and has been successfully established at the University Hospital of Leipzig in March 2013.

The accuracy of the 3D visualisation of the tumor in context to the anatomic structures relies on an appropriate quality of the CT scan. Cancellations on the tumor-associated slices due to metallic foreign material or motion artefacts can make segmentation difficult or nearly impossible. Another issue could be a vague demarcation of the tumor because of inadequate distribution of the contrast agent or perifocal oedema. MRI scans may overcome such limitations and provide a more reliable segmentation especially of the tumor. A currently ongoing project addresses the development of MRI segmentation and image data fusion.

**Future work**

Despite of the aforementioned issues, there is much potential of 3D visualisation, from which the interdisciplinary team as well as the patients can benefit.

Difficult surgical approaches could be planned, and awareness of risk structures like a kinking arteria carotis might be attracted by means of 3D exploration. Furthermore, the 3D visualisation could be used for better demonstration and explanation of individual findings and therapy for the patient.

Although the effort is already justified by the more precise tumor classification, in our opinion, further options should be taken into consideration to raise the overall effectiveness. Therefore, a project on transferring segmented CT data for radiotherapy planning would be useful. With 3D volumetry, a further criterion for reliable response evaluation in neoadjuvant chemotherapy protocols is addressed. Mueller et al. found a higher reliability for volumes estimated by the segmentation-based approach than the widely used diameter-based approach for lymph nodes [20], and the here presented results demonstrate an improved predictability of the exact TNM status and in particular the involvement of lymph nodes by use of the TTM.

As the investigation has been only performed with re-evaluation by otolaryngologists, the investigation must be repeated with physicians from other oncological disciplines and medical experts involved in head and neck tumor boards to prove a common benefit by comprehension of all the clinical data of the particular patient in the TTM.

The intense research on automatic and semi-automatic segmentation algorithms and processes will reduce the preparation time and related costs of 3D model generation.
Fig. 6  Relation of the TNM classification in the re-evaluation and the original diagnosis with and without TTM
Conclusion

The use of a 3D documentation system increases the reproducibility of individual HNC patient data through decreased variance in T and N classification and avoids the deviation of the mean value in lymph node stage. The extra effort needed to aggregate data in the TTM is justified as this method integrates various information, and in particular those which are difficult to imagine if presented singularly or only by means of CT scans. In conclusion, the TTM promises an improved decision-making process due to more precise imaging information within the interdisciplinary tumor board.

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Conflict of interest The authors declare that they have no conflict of interest.

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