Head and Neck: Recurrence versus Scarring
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Background
Head and neck squamous cell carcinoma (HNSCC) is the most common carcinoma to arise in the head and neck. In many centers chemoradiotherapy (CRT) is the treatment of choice for advanced stage HNSCC because it achieves relatively high rates of locoregional control, while producing good cosmetic results and preserving function. However, post-treatment locoregional failures do occur in 25-50% of patients and in this situation patients benefit from early salvage surgery. Unfortunately, the clinical identification of residual cancer is problematic, especially in the early post treatment period. At this time clinical symptoms are inaccurate, endoscopic examination is hampered by post radiation oedema and mucositis, and primary and nodal disease may be too deeply seated to be detectable. In addition biopsies encounter sampling errors and may cause complications such as infection and chondritis. Planned neck dissection following CRT is associated also with morbidity, and as the majority of these patients have negative neck dissection specimens, it is a procedure that is no longer performed routinely.

Therefore, great emphasis is placed on imaging the post-treatment neck to (1) identify residual tumours at an early stage, and (2) identify expected post-treatment changes in order to prevent unnecessary surgery and biopsies. The importance of imaging in the clinical management of the post treatment neck has highlighted the challenges the radiologist faces when attempting to distinguish residual/recurrent tumour from scarring/post treatment inflammation. This lecture will concentrate on the post CRT/RT evaluation of primary and nodal sites in patients with HNSCC, using morphological assessment by MRI. Clinical cases will be used to illustrate the expected post treatment findings, residual/recurrent tumours, and patients with those indeterminate findings that cause a diagnostic dilemma. Functional MRI techniques also will be illustrated and there will be a brief comparison of MRI and FDG PET-CT.

Morphological assessment using MRI

General points
The detection of residual/recurrent tumour by MRI (and CT) depends upon the identification and assessment of the size, shape and contrast enhancement of a residual focal mass, but there is overlap between the appearance of a residual tumour and a benign post-treatment mass (inflammation, oedema, necrosis, scar tissue). MRI has an advantage over CT for characterizing these residual masses by using T1 weighted post contrast images and T2 weighted images. Assessment of T2 signal intensity is particularly valuable in the post treatment assessment because tumours have higher T2 signal intensity than scar tissues. Mature scar tissue forms a flat-edged/retracted mass of low/very low T2 signal (1-3) which is a valuable sign because it can be found even in the early post treatment period. Some useful pointers to aid in the characterization of a
residual post-treatment mass by MRI are listed below. For purpose of this lecture T2 signal intensity is graded as low (≤ muscle); intermediate (> muscle - < fluid); high (fluid).
1. Residual tumour forms an expansile mass with moderate/ (marked) contrast enhancement and intermediate/ slightly high T2 signal. **It is useful to look for focal residual masses that have similar signal intensity on all sequences to the solid component of the pre-treatment tumour.**
2. Inflammation has a variable appearance but often shows greater contrast enhancement and higher T2 signal than tumour
3. Immature scar tissue can have a variable appearance, including similar contrast enhancement and T2 signal to tumour, but it may also have the characteristic low T2 signal while contrast enhancement is still evident.
4. Mature scar tissue forms a flat-edged/retracted mass with no contrast enhancement and low/very low T2 signal.

**Assessment of the primary tumour**
Contrast enhancement and T2 signal intensity of a residual mass on MRI have been used to identify residual/recurrent tumour (4, 5, 6) but the MRI criteria for post treatment assessment are still evolving. A scoring system also has been used for MRI (4, 7, 8) which is based on the CT scoring system first proposed for laryngeal cancer (9). This system divides the post treatment primary site into three scores (1) expected post treatment changes only (no evidence of local failure); (2) focal mass < 1cm or asymmetry (indeterminate findings); (3) focal mass ≥ 1cm (high risk of local failure). Using this system post treatment necks with expected changes only (i.e. no residual mass) by MRI (or CT) have a high NPV for residual tumour. However, when a residual mass is present the PPV can be very variable even when the masses are ≥ 1cm. Further research is clearly needed before the optimum approach to MRI post treatment assessment is defined but in the mean time a method which incorporates the T2 signal intensity of both tumour and scar tissue into the scoring system will be illustrated using clinical cases scanned in the early post treatment period.
(1) No evidence of local failure: (a) no abnormality, (b) no focal mass but expected radiation induced tissue changes which include; concentric symmetrical swelling which involves the mucosa and deeper tissues especially of the larynx and pharynx; retropharyngeal oedema; reticulation in the fat; thickening of the skin and platysma muscle (c) focal mass composed entirely of flat-edged/retracted low T2 signal scar tissue (tumours that had invaded beyond the mucosa into deep tissues nearly always form MRI visible scar tissue).
(2) Indeterminate findings: focal masses <1cm, or masses of mixed signal intensity where none of the components meet the criteria listed in (3). If no tumour is apparent on clinical examination these patients can be followed up by imaging (such as MRI or PET-CT).
(3) High risk of local failure: focal mass ≥1cm which is expansile and has similar signal characteristics on T2W and T1W post contrast to the pre-treatment tumour. MRI identifies the site for biopsy when the tumor is not clinically apparent.
Assessment of nodal metastases

Residual nodal masses are common and assessment can be even more problematic than assessment of primary residual masses. Nodes may have extensive areas of necrosis before treatment which after successful treatment take many months to resolve resulting in a delay in size reduction of the node. In addition metastatic nodes may have extensive extracapsular tumour invasion into adjacent tissues such as the sternocleidomastoid muscle. Currently MRI assessment of residual nodal metastases is based mainly on CT criteria which report a favourable outcome when residual nodes measure $\leq 1-1.5$cm and have no focal abnormality (including necrosis) or extracapsular spread (10-13). Nodes larger than this size or with necrosis are more problematic because the PPV for finding a residual nodal metastasis is low at 30-40% (11), even nodes as large as 5cm can be disease free (14). In practice tiny residual areas of scarring on MRI (subtle retracted areas of scarring are nearly always apparent on MRI if a diligent search is made of the nodal bed) have a high NPV for residual disease, but solid enhancing nodes greater than 1-1.5 cm indicate a high index of suspicion. Predominantly necrotic nodes with a thin rim could represent residual metastatic nodes or slowly resolving sterile nodes, those with thick walls or nodular solid nodules should be regarded with a higher index of suspicion. Ultrasound guided FNAC, PET-CT or follow-up MRI are all options to aid diagnosis in patients in whom neck dissection is not planned. Cases will be shown to illustrate the difficulties encountered in post treatment MRI nodal assessment.

Volumetric analysis (CT/MRI)

The reported percentage reduction in volume that identified residual cancer at the primary site was $< 35\% - < 50\%$ (15, 16) and predicted a negative neck nodal dissection was $> 90\%$ (17). However, in practice greater weighting tends to be put on the morphological appearances rather than the percentage reduction in size.

MRI Surveillance in the head and neck

There is a general consensus that patients at risk of locoregional tumour recurrence (including patients with advanced HNSCC treated by CRT), require imaging surveillance in order to detect residual/recurrent tumour at an earlier time than is possible by clinical assessment alone. The optimum time points for surveillance imaging are under debate but it is known that locoregional failures usually occur within 2-3 years with most cases arising in the first year. Therefore surveillance scans should be more frequent in the first year (every 3-6 months) and less frequent in the next 1-2 years. MRI is ideally suited for surveillance imaging and candidates for salvage surgery after CRT may benefit from the first MRI scan being in the early post-treatment period at about 6 weeks. An early scan detects patients at high risk of local failure and acts as a baseline for the indeterminate cases. Surveillance imaging also affords the opportunity to detect the small number of patients with initially normal follow-up scans who later relapse. Late tumour relapse should always be sort at the margins of the primary tumour bed and in nodal sites that were spared from the high radiation dose field, including those in the opposite side of the neck and in the salivary gland and retropharyngeal regions. Cases will be shown to illustrate the value of MRI surveillance.
**Functional assessment using MRI**

MRI is a very versatile modality providing both anatomical and functional information in the same examination. At present diffusion weighted imaging (DWI) is the most promising functional MRI technique in the head and neck. Residual cancers continue to show restricted diffusion after treatment and this can be identified as high signal intensity on the b 1000 images and low signal intensity on the ADC (apparent diffusion coefficient) maps. When the mean ADC of a residual mass is measured residual cancers have significantly lower ADCs than benign treatment masses (18, 19) even at 6 weeks post treatment (20). These studies have found similar thresholds of around < 1.3 to 1.4 x10^-3 mm^2/s for residual cancers but standardisation of the DWI technique and larger studies are required before ADC thresholds can be implemented in routine clinical practice. At an even shorter post treatment period (3 weeks), DWI has the potential to detect residual cancers based on a significantly lower percentage ADC rise from baseline compared to benign post treatment masses (21). When measuring the ADC it is important to remember to exclude areas of frank necrosis from analysis because these can result in very low ADC readings. Proton magnetic resonance spectroscopy (MRS) has been shown in one study to detect residual cancers based on a persistent choline peak in the mass but whilst the specificity of this technique was high (100%), the sensitivity was low (44%) (22). It is worth noting that currently there is a paucity of data comparing functional MRI techniques to morphological-based MRI or FDG PET-CT, especially in the cases of the indeterminate mass. It should also be noted that after treatment residual tumours become smaller and more irregular in shape and hence may be more difficult to assess in the head and neck by functional MRI. However, reported results from pre-treatment dynamic contrast enhanced MRI (DCE-MRI) (23-25) and intratreatment DWI (20, 26, 27) are even more promising and open up the possibility of predicting treatment response at a much earlier time point.

**FDG PET/PET-CT versus MRI**

Currently FDG PET/PET-CT is considered to be the best technique for identifying residual/recurrent tumour in the post-treatment neck, especially when the examination is performed at least 10-12 weeks after the end of treatment. Pooled data from review and meta-analysis studies have shown that the PPV is in the range of 52-75% (primary site) and 49-59% (node sites) and the NPV for both sites is around 95% (28, 29). The very high NPV of PET suggests it is of value for identifying patients without residual/recurrent cancer, but the lower PPV still means there is diagnostic uncertainty when the examination is positive. There are a few studies, including pooled data from review and meta-analysis studies, which show FDG PET/PET-CT has a higher sensitivity and specificity than MRI for head and neck cancer tumour recurrence (28, 30, 31) but large scale prospective studies with strict diagnostic criteria are needed to confirm these findings. Furthermore MRI has an advantage in surveillance imaging because it does not require the injection of a radioactive substance and it has the potential to be used in the early post-treatment period when PET-CT encounters more false positive and false negative findings. At present the best strategy for imaging the post treatment neck in terms of the imaging modality and optimum timing has yet to be identified, in the future a combination of both modalities may be found to produce the best results.
Summary
The post treatment MRI assessment of HNSCC remains a challenge. MRI has a high NPV for residual disease at the primary and nodal sites, but the diagnostic accuracy falls when an abnormality beyond the normal expected changes is found. In the future improved imaging criteria for treatment assessment, including the incorporation of information from T2 weighted images, and the further development of functional MRI techniques have the potential to rival PET-CT, especially in the early post treatment period. Cases will still be encountered which are indeterminate on all imaging modalities or are initially normal but develop a late marginal tumour recurrence. In these cases MRI is best suited for follow-up/surveillance. Looking to the future the ultimate goal is to predict which patients will not respond to CRT so that treatment regimes can be changed and in this regard functional MRI shows great promise.

References
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