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● *Oncology Imaging*

STAGING AND FOLLOW-UP OF NASOPHARYNGEAL CARCINOMA: MAGNETIC RESONANCE IMAGING VERSUS COMPUTERIZED TOMOGRAPHY

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Purpose: To compare computerized tomography (CT) and magnetic resonance (MR) in relation to their accuracy in the staging of nasopharyngeal carcinoma (NPC); to compare CT and MR in postirradiation follow-up of NPC.

Methods and Materials: Staging: From 1985 to 1993, 53 patients affected with NPC were studied with MR and CT. All cases were biopsy-proved epithelial carcinoma. Plain and contrast-enhanced CT scans were performed with third-generation scanners. Magnetic resonance were obtained with 0.5 and 1.5 Tesla units in sagittal, axial, and coronal planes. Computerized tomography was chosen as reference method and findings obtained with MR were compared to those obtained with CT. Follow-up: From 1985 to 1993, 53 patients irradiated with radical intent were followed up with both CT and MR; 71 examinations were performed in all. The baseline follow-up scan was performed, in general, no sooner than 2 months after the end of radiotherapy. All patients were submitted to unlimited clinical follow-up.

Results: Staging: Magnetic resonance showed retropharyngeal adenopathies in 6 of 14 cases in which oropharyngeal involvement had been reported after CT; in 3 other patients, adenopathies were recognized on MR, while primary extent to parapharyngeal space had been diagnosed on CT initially. Infiltration of long muscles of the neck was revealed with MR in 14 cases. On the other hand, CT showed bone invasion in 12 patients vs. 8 on MR. Upstaging to T4 occurred in four cases on the basis of CT; no upstaging occurred after MR. Follow-up: Findings on CT were uncertain in 10 out of 53 patients, disease recurrence was excluded by MR in nine cases, whereas progressive disease was confirmed in one patient.

Conclusion: Staging: Our series shows that either CT and MR can provide essential information in the staging of NPC. Magnetic resonance, however, seems to provide the most detailed imaging of soft tissue invasion outside the nasopharynx and of retropharyngeal node involvement. Nonetheless, its limitations in evaluating bone details suggest that CT should be always performed when the status of base of skull is uncertain on MR. General reasons and our data indicate that CT can still be considered a valuable tool in routine NPC staging. Follow up: Magnetic resonance may be the modality of choice because it seems to solve, more often than CT, the problems of differentiation between postradiation changes and recurring tumor, apart from those cases showing subtle bone erosions on initial CT scan.

Nasopharyngeal carcinoma, Computerized tomography, Magnetic resonance.

INTRODUCTION

Accuracy in pretreatment staging of patients affected with nasopharyngeal carcinoma (NPC) represents the basic step to successful treatment; since the mid-70s, computerized tomography (CT) has led to far better staging than conventional politomography and, following, to more refined treatment planning. Improved 5-year local failure-free rates reported in the international literature (1, 7, 12) in comparison with older series may be ascribed, at least partially, to the incorporation of data provided by CT in

treatment planning. When we reviewed our series in 1991, a group of 143 patients staged without CT was compared with a group of 165 patients staged with CT; 5-year local control was significantly higher in the latter group (72% vs. 47%) (13).

With the advent of magnetic resonance imaging (MR) in the mid-80s, a new extraordinary tool was added to the diagnostic paraphernalia. Its role in the initial assessment of head and neck tumor extent is still under evaluation; MR may be the method of choice in NPC staging according to some authors (8, 9, 22). However, the deci-

sion whether to primarily use MR rather than CT is often subtle and controversial because the two modalities have different potentialities when sites and subsites of these anatomic regions are studied (5, 9, 10, 20, 21). The role of MR in the follow-up is even more uncertain due to the difficulty of differentiating postradiation changes from locally recurrent NPC (2, 3, 9).

In the present article, we report the results of a trial aimed at finding out advantages and drawbacks of CT and MR staging of NPC in relation to their respective ability of showing the involvement of sites and subsites of the nasopharynx and adjacent spaces. The available follow-up observations have been reported in the present study as well.

METHODS AND MATERIALS

Staging

From January 1985 to June 1993, 53 patients affected with NPC were studied with MR and CT; 42 patients were male and 11 were female. Their ages ranged from 18 to 71 years (mean age 50 years). All cases were biopsy-proved epithelial carcinoma. All patients were irradiated with curative intent at the Department of Radiotherapy, Florence, Italy, except three patients who had distant metastases at presentation.

Plain and contrast-enhanced CT scans were performed on third-generation scanners; 100–150 ml of iodinated contrast agents were injected i.v. In addition to axial scans, coronal scans were performed whenever possible, with the patient lying supine or prone. Basic technical parameters are reported in Table 1.

Magnetic resonance images were obtained with 0.5 and 1.5 Tesla units in sagittal, axial, and coronal planes. A spin-echo technique was used; other basic technical parameters are reported in Table 1. Only eight patients had MR imaging before and after the injection of Gadolinium (Gd-DTPA) due to the fact that the restrictions placed by the Italian legislation on paramagnetic contrast agents in the extraneurological field were only recently abolished.

An accurate assessment of disease spread was performed with both MR and CT, and the involvement of nasopharyngeal sites and adjacent anatomic structures was examined in detail. All original films were reviewed by two radiologists. Due to our longer work experience with CT, computerized tomography was chosen as the reference method. Consequently, the findings obtained with MR were compared to those obtained with CT, site by site, to discover concurrence and discordance between the two staging methods.

Follow-Up

From January 1985 to June 1993, 53 patients irradiated with radical intent at the Radiotherapy Department of Florence were followed up with both CT and MR. The composition of this group was the following: 40 patients were male and 13 were female. Age ranged from 18 to

Table 1. Basic technical parameters used in the present series for performing CT (with a third generation scanner) and MR

| |
|-------------------------------------------------------|
| CT |
| Slice thickness 4.5 to 6 mm |
| Slice factor 1 (continuous scanning) |
| 400 to 480 mA (high-detail work) |
| 120 kV |
| Field of view (FOV) 200 to 240 mm |
| Large focal spot |
| Scan time 4.8 s |
| MR—T ₁ -weighted images |
| 7 to 9 slices |
| Number of excitation (NEX): 4 |
| Repetition time 580 ms |
| Echo time 30 ms |
| Scan time 5 to 6 min |
| MR—T ₂ -weighted images |
| 11 to 13 slices |
| NEX: 2 |
| Repetition time 2000 to 2100 ms |
| Echo time 50 and 100 ms |
| Scan time 11 to 13 min |
| MR—T ₁ and T ₂ -weighted images |
| Slice thickness 6 to 8 mm |
| Slice factor 1.1 |
| FOV 240 to 250 mm |
| Matrix 256 × 256 |
| Pixel size 1 mm |
| Head and neck receiver coils |

68 years (mean age 47 years). Thirty-seven patients were part of the group of the 53 patients previously staged with both modalities; the other 16 patients were already in follow-up before 1985 and were submitted to simultaneous CT and MR mainly to detect late posttreatment changes (12 patients), to clarify findings that were uncertain on CT, or to substantiate a doubt about possible disease recurrence (in 4 patients). Some patients had their examinations repeated twice or more so that an overall number of 71 CT and MR scans were performed in 53 patients. Generally, baseline follow-up scans were performed 2 to 3 months after the end of treatment. Due to the life-long follow-up policy pursued at our institute, all diagnoses were confirmed by data provided by clinical follow-up and validated with biopsies in those cases in which a local relapse was diagnosed or strongly suspected.

RESULTS

Staging

A detailed analysis of results obtained in the staging is reported in Table 2. Computerized tomography and MR findings are fully in agreement in relation to disease limited to the nasopharyngeal cavity, whereas differences of various degrees can be noticed when assessing disease spread beyond the boundaries of the nasopharynx. Actually, there is little disagreement in those cases in which there was anterior extent into the choanae or into the nasal cavities and the maxillary sinuses, lateral invasion of the

Table 2. Fifty-three patients affected with NPC and staged with CT and MR: Distribution of involved sites and subsites by imaging modality

| | CT | MR |
|--------------------------|---------------------|---------|
| Site/subsite | | |
| Vault/posterior wall | 44 | 44 |
| Lateral wall | 52 | 52 |
| Choanae/nasal cavity | 20 | 19 |
| Oropharynx* | 14 | 8 |
| Parapharyngeal space | 30 (+1) | 31 |
| Long muscles of the neck | — | 14 (+1) |
| Base of skull | 12 | 8 |
| Middle cranial fossa | 2 | 2 |
| Sphenoid sinus | 4 | 4 |
| Ethmoid | 3 | 3 |
| Maxillary sinus | 6 (+2) [†] | 6 |
| Lymph nodes* | — | 6 |

(+n): uncertain findings.

* Oropharyngeal extent on CT was recognized as lymph node metastases on MR in six patients.

[†] Two uncertain findings on CT were interpreted as obstructed rather than invaded sinuses on MR.

parapharyngeal spaces, and upper spread into the ethmoid and sphenoid sinuses. On the contrary, disagreement is substantial for lower extent to the oropharynx, the posterior infiltration of long muscles of the neck, and the upper invasion of the base of skull. In fact, MR showed that there were retropharyngeal adenopathies in 6 out of 14 cases in which oropharyngeal involvement had been reported after CT; the ability of MR to discriminate between the primary tumor and closely adjacent lymph node metastases was confirmed in three additional patients where the initial diagnosis of direct tumor invasion on CT was changed after lateral retropharyngeal adenopathies were recognized. Furthermore, MR showed a completely new potential for revealing infiltration of the long muscles of the neck (14 cases vs. none on CT). However, CT proved better than MR at displaying involvement of the base of skull (12 cases vs. 8 on CT).

All cases were classified according to the UICC (International Union against Cancer) TNM Staging System—1987 (6) on the grounds of the findings of CT, MR, and of clinical examination; CT staging of the primary, as compared to MR staging, upstaged four cases from T3 to T4 owing to bone erosion of the base of skull. No lesions were upstaged with MR; however, we think that in one case, a T2 lesion might have been upstaged to T3 because infiltration of the long muscles of the neck detected on MR. Although these muscles are not considered by the TNM classification, it may be reasonable to classify their invasion as T3, as they are definitely extranasopharyngeal and in this respect their infiltration corresponds to spreading to the parapharyngeal spaces.

Follow-Up

No evidence of local disease was detected on CT and MR in 25 patients (40 examinations in all, some patients

had repeated examinations). Findings on CT were uncertain in seven patients: disease recurrence was excluded after MR and confirmed by follow-up. The cases were classified as posttreatment changes or scarring phenomena. Four cases showed nonspecific obstruction of maxillary (3)-ethmoid (1) sinuses on CT that could be easily recognized as “inflammatory”; all of them are currently without evidence of disease. Tissue of parenchymal density on CT was found within the sphenoid sinuses in one patient (initially staged T4 for bone involvement) that was defined as “inflammatory” with MR. The patient was carefully followed up with repeated examinations and developed a basicranial recurrence 15 months after the first examination (20 months after the end of radiotherapy); the patient was reirradiated and was alive and well at the last follow-up visit 54 months after the first treatment. In two additional patients, CT showed nasopharyngeal wall thickening and asymmetries suggesting a possible relapse; the two cases were diagnosed as posttreatment sequelae and have not developed a recurrence so far. Thirty-one out of 32 patients in all, in whom MR was considered negative, with a median follow-up of 5 years (mean 5.6 years, range 1 to 20 years), are continuously disease free.

Computerized tomography and MR showed obvious persistence or recurrence of local disease in 18 patients (21 examinations). In one case, MR helped to define the real disease extent better than CT, excluding the invasion of maxillary sinuses. One patient with an advanced lesion extensively involving the base of skull showed high signal intensity in T₂-weighted MR images that was initially regarded as suggestive of disease persistence. However, the biopsy was negative and the patient is still alive with no signs of progressive disease 4 years later; the signal is supposed to be due to a slowly repairing lesion. Findings on CT were uncertain in three patients. In the first case, tissue of parenchymal density on CT within the sphenoid sinuses was diagnosed as a malignant regrowth with MR. In the second case, the anterior spread to nasal cavity was presumed on CT, but was not confirmed on MR; however, MR confirmed the relapse. A small mucosal bulging on CT suggested a possible relapse in the third case. Although MR had confirmed the finding, a subsequent biopsy turned out to be negative; nevertheless, the patient developed an aggressive local recurrence 20 months later and could not be salvaged. In summary, 20 out of 21 patients in all, in which MR diagnosed persisting or recurring disease, were validated through biopsy. Seventeen out of the 20 local relapses occurred within 24 months. Fifteen patients have died of disease and 5 are alive with progressive disease.

DISCUSSION

Staging

When staging NPC, it is important to assess as accurately as possible the real disease extent to tailor treatment

Table 3. CT vs. MR: Advantages and disadvantages

| | Contrast-enhanced CT | Plain MR |
|-----------------------------------------------------------|----------------------|----------|
| Availability | ++ | — |
| Waiting lists | — | + |
| Easiness of performance | + | — |
| Length of examination | + | — |
| Operating expenses | — | + |
| Comfort* | — | — |
| Claustrophobia | — | ++ |
| Motion artifacts | — | ++ |
| Artifacts due to implanted dental prosthesis [†] | + | ++ |
| Absolute contraindications [‡] | + | ++ |
| General anesthesia/continuous monitoring [§] | + | — |
| Spatial resolution | + | — |
| Contrast resolution | — | + |
| Bone detail | + | — |
| Calcifications | ++ | -- |
| 3D assessment | + | ++ |

* Patients positioned for coronal scans often feel uncomfortable.

[†] Metal prosthesis cause artifacts on coronal CT scans.

[‡] Monoclonal gammopathy for CT; ferromagnetic clips/pacemakers for MR.

[§] Routine ferromagnetic anesthesiologic devices cannot be used when performing MR.

volume and technique—otherwise, local control could be adversely affected (13). Furthermore, the accurate assessment of disease extent makes it possible to identify the more advanced cases whose local control rate is not always satisfactory; such patients might be candidates for more aggressive radiotherapy (18) or concomitant chemotherapy (16).

Computerized tomography and MR have respective specific advantages and disadvantages (Table 3). According to the data of the present series, MR seems to provide a more accurate evaluation of the extent of the primary tumor; in fact, MR is able to identify as retropharyngeal nodes findings previously misdiagnosed on CT as oropharyngeal or parapharyngeal invasion. Moreover, it provides new pieces of information such as the infiltration of long muscles of the neck and pterygoid muscles that, in most cases, cannot be clearly imaged with CT; according to some authors, MR can also detect cavernous sinus (9) and early perineural invasion as well. However, we cannot disregard the fact that, in our series, upstaging from T3 stage on MR to T4 stage on CT (due to the detection of bone erosion) was remarkable. On the other hand, the advantages of CT over MR in imaging bone details, especially when the bone contains little or no fat marrow, are well known (9, 11). This suggests that CT should continue to be part of the pretherapeutic workup whenever the base of skull involvement is suspected or possible, but not clearly detected with MR. In fact, upstaging leads to a substantial change of treatment volume and

may hint that a locally aggressive treatment should be delivered.

As most patients affected with NPC are clinically node positive at presentation, the contribution of modern imaging (CT/MR) seems to be quite limited, as far as lymph node involvement is concerned. However, the above-mentioned MR unique ability of differentiating between retropharyngeal nodes and the primary tumor, information that is often missed on CT, should be mentioned. A small number of patients, once classified as cases with oropharyngeal or parapharyngeal invasion, might be reclassified as node positive. As for parapharyngeal invasion, Teo (18) hypothesized that retropharyngeal node metastases, not identified on CT, might well have accounted for the significant predictive value of the parapharyngeal disease with relation to the occurrence of distant metastases in his series. Actually, there is universal agreement on the fact that node-positive patients are at high risk of developing distant metastases (4, 7, 17, 19), and that 30% to 50% of patients with NPC will later develop and ultimately die from distant metastases (7, 14, 15).

Due to our limited experience, the role of paramagnetic contrast agents has not been discussed in the present study. Information on this topic is scarce in international literature as well; according to Vogl et al. (23), MR with Gd-DTPA should not be recommended when large tumors are well delineated because of the increased cost and longer examination time. The latest contributions of technology to MR, not used in the present investigation, that hold promise of further increasing the potentials of MR, should also be mentioned.

Follow-Up

The primary need of a clinician during the aftercare of NPC is to differentiate between postradiation changes and residual/recurring disease. On the basis of our data, we think that MR may help to solve problems of differential diagnosis more often than CT. However, there are many pitfalls because of the fact that both postradiation changes and the tumor are not immobile entities, but rather evolving processes.

The pathways leading to radiation fibrosis are fairly clear and, in broad terms, an "early" scar can be distinguished from an "old" mature scar. The early scar consists of a well-hydrated granulation tissue with a rich cellularity and vascularity; therefore, its signal on T₂-weighted images is bright. Mancuso (9) reported that both granulation tissue and persistent tumors have a greater signal intensity than that of the muscle and show enhancement on contrast-enhanced MR. As a result, they are not distinguishable. This is why a baseline scan intended for follow-up purpose should be obtained 2–3 months after the end of treatment when massive acute postirradiation changes subside. On the contrary, an old scar is mainly a dehydrated, hypocellular, and collagenous tissue with a low signal on T₂ MR scans. Held and Hobletter (3) pointed out that the scar shows a lower signal intensity

than the tumor in T₂-weighted images, depending on its age. In fact, "mature" fibrosis has different vascularity and cellular content than the tumor, which explains its lower intensity signal on T₂-weighted images. Mancuso confirmed that end-stage fibrosis is isohypointense to muscle on MR (9).

Unfortunately, the previous description of a mature scar does not always correspond to what is observed after radiotherapy because there may be reactive mucosal and submucosal changes, tissue edema, and teleangectasias persisting for months or longer; changes may be permanent after the high doses (~ 70 Gy) that are given to NPC. In these cases, signal intensity, which is correlated with the variable degree of vascularity, cellularity, and water content, may actually show bright intermediate to high signal intensity in T₂-weighted MR images many months or even years after treatment, as we have observed in our series. We have also noticed that residual/recurrent disease may be hypointense in comparison to granulation tissue during the second to third month and to changes following radiation in PD and T₂-weighted MR images as well.

In our opinion, the analysis of signal intensity may be suggestive of disease relapse, but without rigid absolutes because the pattern of signal may change according to a wide variety of parameters (total dose of radiotherapy, age of "scar," vascularity and cellularity of tissues, anatomic site, and size of the primary). Indeed, there is a general agreement (2, 3, 9) that the signal intensity pattern is not specific and that a diagnosis of recurrent tumor cannot be established on the basis of signal intensity in itself. Both signal characteristics and morphology must

be taken into account before putting forward a solid suspect of relapse, and histologic confirmation is needed as well. In any case, a strict cooperation between the radiologist and the oncologist is essential and any information provided by CT and/or MR must be integrated with data coming from clinical follow-up.

CONCLUSIONS

The analysis of our series shows that both CT and MR can provide essential information in the staging of NPC. Availability, easiness of performance, and operating expenses are all in favor of CT. Magnetic resonance, however, seems to provide the most detailed imaging of soft tissue invasion outside the nasopharynx and of retropharyngeal nodes. Nonetheless, its limitations in evaluating bone details suggest that CT should always be performed when the status of the base of skull is uncertain on MR. Considering both the general reasons and the data from the present article, it is our opinion that CT can still be considered a valuable tool in NPC staging in routine clinical practice; MR, as a second-line exam, may be reserved to selected presentations in which the aforementioned potentials of MR (assessment of retropharyngeal adenopathies, infiltration of muscles, etc.) can be helpful.

As far as follow-up is concerned, the basic clinical question of differentiating between postradiation changes and recurring tumor seems to be less often uncertain with MR than with CT. Therefore, MR, even if not a panacea, may be the preferred modality. However, the cases with subtle bone erosions or cortical defects on staging CT are probably best followed up with this modality.

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