COMMENTARY

PROBLEMS IN THE CURRENT TNM STAGING OF NONMELANOMA SKIN CANCER OF THE HEAD AND NECK

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Nonmelanoma skin cancer (NMSC) is the most common malignancy encountered in the white population, and more than a million new cases are expected annually in the United States alone.\(^1\) Overall, 75% arise in the head and neck region,\(^2\) approximately 80% are basal cell carcinoma (BCC) and 20% are squamous cell carcinoma (SCC) cases. Nearly half of the patients are over the age of 65 and 25% have multiple lesions. The incidence of SCC increases more rapidly with age and cumulative sun exposure than does that of BCC, is far more common in the older age group, and is more common in men than in women.\(^3\) The incidence of NMSC is increasing and age at initial presentation is decreasing.\(^3,4\) Other than sun exposure, host factors, medical syndromes, and environmental exposure were reported to be associated with increased incidence of NMSC.

Countries with fair-skinned populations and excess sun exposure, such as Australia and Israel (ranking 1 and 2, respectively, in the incidence of skin cancer) are particularly prone to this type of neoplasia, reaching what was described as epidemic proportions.\(^5\)

Skin cancer is usually noted early even if not necessarily recognized as such, and often a prolonged period of time elapses before a definite diagnosis is reached. The median delay between occurrence of initial symptoms and presentation is reported to be 3 years.\(^4\) Many of the patients with skin lesions tend to try different remedies, some of which may favorably affect or alter the appearance of the lesions to an extent, and this may lead to further delay.

Although the majority of NMSCs occur in sun-exposed skin and thus appear in readily observed areas, a significant number of patients present with advanced invasive disease, not infrequently accompanied by regional metastases. This may be due to a multitude of reasons: lack of awareness of the significance of local recurrence by either physician or patient, late detection of recurrent or residual disease, lack of adequate follow-up, failure to associate a neck or parotid mass with a skin lesion, an abundance of other skin lesions, the availability of fluorouracil cream treatment, and, of course, denial. Also, proximity to structures such as the eye or ear may generate reluctance to

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radically excise the tumor, leading to not only residual disease or early recurrence but disease that may readily invade the orbit or the middle ear and temporal bone. This “foot dragging” may also stem from the shared notion in the general public that skin cancer is “not dangerous.” Marcil and Stern\(^6\) reviewed 17 studies and found the overall 3-year cumulative risk of a subsequent SCC after an index SCC to be 18\%, at least a 10-fold increase in incidence when compared with the incidence of first tumors in a comparable general population. For BCCs, the 3-year cumulative risk was 44\%, also at least a 10-fold increase in incidence compared with the rate in a comparable general population. What is surprising is that neglected tumors are frequently incurred in patients with a documented history of NMSC who should be well aware of the possibility of skin cancer and should definitely know better.

The current TNM staging for NMSC (excluding eyelid, vulva, and penis) is as follows: Tx, primary tumor cannot be assessed; T0, no evidence of primary tumor; Tis, carcinoma in situ; T1, tumor \(< 2\) cm in greatest dimension; T2, tumor \(< 2\) cm but \(< 5\) cm in greatest dimension; T3, tumor \(< 5\) cm in greatest dimension; T4, tumor invades deep extradermal structures (e.g., cartilage, skeletal muscle, or bone); Nx, regional lymph nodes cannot be assessed; N0, no regional lymph node metastasis; N1, metastasis to nearby lymph nodes; Mx, presence of distant metastasis cannot be assessed; M0, no distant metastasis; M1, distant metastasis is present; stage 0: Tis, N0, M0; stage I: T1, N0, M0; stage II: T2 or T3, N0, M0; stage III: T4, N0, M0 or any T, N1, M0; and stage IV: any T, any N, M1. Thus far, the current staging system has been challenged or even ignored with regard to the N classification, whereas the T classification has for the most part remained uncontested. Yet the current staging poses several problems in NMSC of the head and neck. Up to T3, the staging relates to tumor 2-dimensional size only. Paradoxically, while by definition a T3 tumor can involve a very large surface area, a minor tumor involving the ear or nasal cartilage is defined as T4. A high number of tumors are recurrent, and many patients have multiple possible primaries in cases of metastases. Also, delayed metastases in skin cancer of the head and neck are not uncommon,\(^7\) and when evaluating a person with a typical “farmer’s skin,” the origin of the metastatic disease is difficult if not impossible to discern. Indeed, in 1 large study, 27\% of patients did not have an identifiable index lesion.\(^8\) The question of identifying which tumor is the origin of metastases does not necessarily complicate the therapeutic approach but does confound the staging system. Veness et al,\(^8\) in a study of 266 NMSC patients with metastatic lymph node disease, concluded that the TNM staging system fails to prognosticate for patients with SCC. Size alone was found to be a poor predictor of outcome, because the majority of patients in their study had T1 lesions. Lesions in the parotid drainage areas or basins with a thickness of 4 to 5 mm were at risk of metastasizing to lymph nodes, and recurrent lesions increased this risk.\(^8\)

Unlike in most cases of staging of head and neck tumors, in which a T4 lesion is automatically advanced to stage IV, a T4 NMSC with N1 (by current staging) neck disease is defined as stage III only. In fact, only distant metastases promote NMSC to stage IV. This is not reflective of the actual clinical situation commonly encountered. Further, in the current TNM staging of other head and neck sites, a subdivision of stage IV to IVa and IVb (resectable vs nonresectable) is often warranted; yet this does not even optionally apply to cancer of the skin.

A distinction should be made between superficial invasion such as of the nasal and auricular cartilages and deep structures such as the temporal bone, orbit, etc. These are currently grouped together and upstage many of the nasal and auricular cancers with minimal cartilaginous involvement to T4 stage while, in fact, the influence of this local invasion on survival is negligible.

Neck disease is a major factor in survival correlating with tumor burden in regional lymphatics reflected in the N staging system.

Nodal metastases from NMSC were significantly associated with recurrent lesions and the following histopathologic features: lymphovascular invasion, inflammation, poorly differentiated histology, invasion into the subcutaneous tissues, perineural invasion, and larger size.\(^2\) The issue of metastatic disease currently addressed by N0 or N1 leads to marked heterogeneity and does not seem adequate for head and neck tumors. This was well demonstrated by Andruchow et al,\(^9\) who stated that the N1 staging classification, as currently used, “would apply equally to a patient with a single 2-cm parotid metastasis, a patient with a 6-cm parotid metastasis and facial nerve invasion, or a patient with metastatic disease in both the parotid and the neck.”

Indeed, in published literature from large oncologic centers, the N1–N3 system is used.\(^10,11\) We also used the N1–N3 system for lack of a better clas-
classification in more than 100 patients with invasive skin cancer, over 50 of whom had regional metastases, and found it to be far more relevant than the current one.

O’Brien et al\(^{12}\) suggested an alternative staging system. Their study demonstrated that patients with metastatic cutaneous SCC in both the parotid gland and neck have a significantly worse prognosis than those in the parotid gland only. Those with cervical nodes >3 cm in diameter or with multiple positive neck nodes had a significantly worse prognosis than those with only a single positive node. The extent of metastatic disease in the parotid gland correlated with the local control rate. The authors\(^{12}\) recommend that the clinical staging system for cutaneous SCC of the head and neck should separate parotid and neck disease.

Andruchow et al\(^{9}\) reported results of a multicenter study, suggesting a revised classification of nodal status. This incorporates a separate staging for parotid and neck nodes and seems a well-founded improvement on the current system. Neck nodal staging is suggested as N1 for single ipsilateral neck node up to 3 cm in diameter and N2 for a single node >3 cm in diameter, multiple nodes, or contralateral nodes. Despite this suggested N1–N2 system that is certainly a step in the right direction, the classic N1–N3 system should also be considered, not just for the sake of uniformity. To underscore this point, a patient with N3 disease of the neck with a mucosal head and neck primary tumor is automatically categorized as having stage IV disease, and the average 2-year survival rate, considering all head and neck sites, is approximately 20%. This is because size larger than 6 cm is associated with a high incidence of extracapsular and distant spread, leading to reduced survival. It is doubtful that the rules that apply to all other head and neck localizations differ in skin cancer of the head and neck. This should, however, be studied further. Also, in advanced metastases involving the parotid gland, defining whether the mass involving the skin is a parotid metastasis involving the skin or a skin lesion involving the parotid\(^ {13}\) is challenging. The current AJCC system stages an N3 metastasis from a parotid malignancy as stage IVB. This should not, however, be confused with a metastasis to the parotid or with those involving it.

A separate staging is provided for skin cancer of the eyelid, vulva, and penis. With an individual staging system for these uncommon localizations, a specific TNM staging for the head and neck region, which accounts for 75% of NMSCs, is essential and is the practical decision. The TNM staging system should be modified according to statistically based large-scale research.

Inclusion of perineural invasion, considered as another adverse prognostic factor, should be considered in the final pathologic staging.

In conclusion, NMSC is the most common malignancy encountered worldwide, with the majority of cases being superficial, recognized early, and properly addressed. Although only a small fraction of cases present with locally aggressive and metastatic disease, the numbers fail to significantly decrease despite preventive efforts. The staging system incorporating both the T and N classification should be totally revised in accordance with the high incidence in the head and neck, to provide the optimal tool for classifying and treating these patients.

**REFERENCES**