Emerging Trends and Treatment Approaches in Nonmelanoma Skin Cancer: A Canadian Perspective

Paul Kuzel, Jeremy B. Green, and Andrei I. Metelitsa

NONMELANOMA SKIN CANCERS (NMSCs) represent the most common form of malignancy in humans, and despite increased public awareness and skin cancer prevention efforts, studies from around the world indicate that there has been a significant increase in the incidence of NMSC in recent decades.[1–9] Despite encompassing a multitude of rare primary cutaneous neoplasms, such as adnexal tumors, dermatofibrosarcoma protuberans, sebaceous carcinoma, Merkel cell carcinoma, and others, the term *NMSC* is usually used to define the two most common subtypes, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).[10]

Although we use this definition of NMSC as well, it is important to note that clear differences exist in the etiopathogenesis and clinical course of BCC and SCC. For instance, although both share many common risk factors, such as geographic location, ethnicity, age, and occupation, recent studies have established differences in the patterns of ultraviolet (UV) exposure, which lead to the development of BCC and SCC.[11,12] Whereas BCC is most likely to develop in individuals exposed to ultraviolet B (UVB) radiation in a brief, intermittent pattern, as is the case with indoor tanning or holiday exposure, the risk of SCC development is related to UV exposure in a linear dose-response fashion, consistent with the fact that the incidence of SCC doubles with each 8 to 10° decline in geographic latitude.[13,14] On a molecular level, the finding that individuals suffering with basal cell nevus syndrome carry a mutation in a gene that codes for a transmembrane receptor known as *PATCHED1*, which negatively regulates the Hedgehog (Hh) signaling pathway, has led to the implication of aberrant Hh signaling as the primary underlying cause of BCC.[15] The transcriptional profile of SCC, on the other hand, reveals alterations in the expression of epidermal growth factor receptor (EGFR), *p53*, and other key modulators of cell survival and apoptosis.[13,16] Finally, whereas BCC is a slow-growing neoplasm with an extremely low rate of metastasis, in the range of 0.0028 to 0.55%, SCC is typically viewed as a more aggressive lesion, with a reported rate of metastasis ranging from 0.5 to 6%.[13,14]

The rising incidence rates and resultant increases in patient morbidity, health care costs, and other negative societal impacts associated with BCC and SCC have generated a great deal of interest in both the further characterization of current epidemiologic trends and the pursuit of novel therapeutic options for the treatment of NMSC. The aim of this article is to summarize the most current available epidemiologic data for NMSC, with a focus on Canadian as well as US statistics. Then the current mainstays of NMSC treatment are outlined before several cutting-edge and investigational treatment strategies are discussed.

Epidemiologic Trends

There is no question that the incidence of NMSC has increased significantly in recent decades, although there is some evidence in the literature that these rates are beginning to stabilize.[3,17] For example, an analysis of NMSC incidence rates in British Columbia, Canada, from 1973 to 1987 reported an increase in BCC incidence of 60.6%

From the Department of Medicine, University of Alberta, Edmonton, AB; Department of Dermatology, University of Miami Miller School of Medicine, Miami, FL; and Division of Dermatology, Department of Medicine, University of Calgary, Calgary, AB.

Address reprint requests to: Andrei I. Metelitsa, MD, FRCPC, Suite 206, 4935 40th Avenue NW, Calgary, AB T3A 2N1; e-mail: andrei.metelitsa@gmail.com.

DOI: 10.2310/7750.2011.00003

DECKER

in men and 48.4% in women, whereas SCC incidence increased by 59.2% in men and 67.4% in women.[18] Demers and colleagues analyzed NMSC incidence in Manitoba, Canada, from 1960 to 2000 and determined that the incidence rate of BCC and SCC in the period 1996 to 2000 compared to the period 1960 to 1964 increased by 182% (men) and 179% (women) for BCC, as well as 266% (men) and 215% (women) for SCC.[1]

However, at least two more recent Canadian epidemiologic studies have reported stabilization in NMSC incidence rates.[17,19] In the evaluation of NMSC incidence in New Brunswick, Canada, from 1992 to 2001, despite continuing increases in BCC incidence in both sexes and increased incidence of invasive SCC in men, there was a plateau in female SCC incidence during the time period of the study.[19] In the largest Canadian population-based analysis of NMSC incidence to date, involving nearly 100,000 patients diagnosed between 1988 and 2007 in Alberta, Canada, a convincing trend toward stabilization of BCC, invasive SCC, and SCC in situ incidence rates was noted.[17] Although sharp increases were initially seen with all three NMSC subtypes, the incidence rate of both BCC and SCC in situ peaked in 2000, whereas the incidence of invasive SCC peaked 5 years earlier in 1995. In addition, an interesting finding that indicates that this stabilizing trend may be due in part to earlier skin cancer detection is the fact that the ratio of invasive to in situ SCC decreased from 1.90 in 1990 to 1994 to 1.36 in 2000 to 2004.

By contrast, studies from the United States seem to unequivocally indicate a continuing NMSC epidemic. For instance, Karagas and colleagues reported that from 1979 to 1994, the state of New Hampshire saw a 235% increase in BCC incidence in men and a staggering 350% increase in women, with smaller increases of about 80% in SCC incidence seen in both sexes.[2] A more recent estimate of incidence rates in the United States comes from a study that analyzed Medicare claims data for skin cancer–related procedures.[4] Using this approach, Rogers and colleagues estimated that in 2006, over 2.1 million people in the United States were treated for NMSC.[4] When compared to an estimate of 0.9 to 1.2 million cases of NMSC in the United States in 1994, this figure would suggest an approximate twofold increase in NMSC during this time period. One study noted that from 2002 to 2006 alone, there was approximately a 16% increase in the rate of NMSC-specific procedures, with an additional increase of over 5% from 2006 to 2008.[3] In all, it has been estimated that in 2007, approximately one in five 70-year-olds living in the United States had at least one occurrence of NMSC, with most of those individuals having been affected numerous times.[20]

Despite the contrast of incidence rates in Canada and the United States, it is clear that continuing efforts to advance public education and awareness of risk reduction and skin cancer prevention strategies can enhance management of this largely preventable disease in both countries.

Current Treatment Approaches

Current treatment protocols for BCC and SCC differ due to their varying pathogenesis and clinical course. However, treatment options for both include a combination of surgical and nonsurgical interventions, with factors such as histologic subtype and anatomic location dictating the optimal strategy.

Surgical management of NMSC remains the most definitive treatment option in terms of recurrence prevention, with Mohs micrographic surgery (MMS) being the gold standard. For excision of primary BCCs and SCCs, MMS has an overall recurrence rate of approximately 1 and 3%, respectively, which is superior to the rate obtained with any other treatment modality, including standard excision, curettage and desiccation, radiotherapy, or cryotherapy.[13,14] Compared to conventional excision specifically, MMS has several key advantages. For example, in a randomized controlled study directly comparing the efficacy of MMS to conventional excision, a fivefold decrease (2.4 vs 12.1%) in the recurrence rate of facial BCC was achieved with MMS.[21] For treatment of recurrent BCC and SCC, MMS delivers a significantly lower risk of further recurrence.[13,22] Several characteristics of SCC make MMS the optimal treatment option, including its propensity for perineural invasion, which is a key risk factor for subsequent recurrence or metastasis.[23] MMS offers the distinct advantage of being able to follow this invasion until full clearance of the tumor is achieved, lowering the risk of potentially lethal metastatic spread. Because of these and other advantages, such as tissue sparing and superior cosmesis, there are several specific indications for MMS in the treatment of NMSC, some of which include a high-risk or cosmetically sensitive anatomic location (nasal tip, eyelid, lip, ear, nail bed), immunosuppression (as in transplant recipients), large or recurrent tumors, or indistinct clinical borders.[13,14]

Imiquimod is a topical agent currently approved in both Canada and the United States for the treatment of low-risk,

superficial BCC, typically with a maximum tumor diameter less than 2 cm and not located on the face. Imiquimod has also proven to be effective in the off-label treatment of several other NMSC subtypes, including nodular and infiltrative BCC, as well as SCC in situ and even invasive SCC.[24] In terms of superficial BCC treatment, various studies have reported clearance rates of 43 to 100%, with the highest clearance rates achieved in studies with more frequent dosing schedules of at least five applications per week.[25] The most common adverse effects reported in these studies were local skin reactions, including erythema, pruritus, and pain.

5-Fluorouracil (5-FU) is a topical pyrimidine antimetabolite that inhibits deoxyribonucleic acid (DNA) synthesis, and there is evidence for its efficacy in the treatment of superficial BCC, SCC in situ, and actinic keratoses. However, it is important to note that 5-FU does not appear to be an effective monotherapy agent for NMSC with invasive features. A study assessing the treatment of 103 patients with invasive BCC using topical 5-FU found that despite the disappearance of any clinical signs of disease in 25% of patients, all continued to have histologic evidence of invasive disease.[26]

Interferons (IFNs) are cytokines that work by binding to receptors on target cells. Intralesional IFN-α2b, used in the treatment of BCC, SCC in situ, and invasive SCC, has been reported to have clearance rates between 70 and 100% in the literature.[25] However, due to factors such as a more serious side-effect profile, cost, and the need for multiple patient visits for IFN injections, its use may be practical only in patients with high-risk and/or invasive SCC.

Electrodesiccation and curettage (ED + C) and cryotherapy are other treatment modalities to be considered for nonfacial superficial BCC and low-risk SCC. Recurrence rates of only 7.7 and 3.7%, respectively, have been reported with ED + C treatment of these two tumor types, although outcomes are highly user dependent.[13,14] When adjuvant imiquimod therapy is used after ED + C for treatment of nodular BCC, improvements are seen in both the frequency of residual tumor and subsequent cosmesis.[27] Although cryotherapy can be used in the treatment of superficial BCC and SCC in situ, with potentially high cure rates, the method does have some disadvantages, including the absence of histologic confirmation of tumor removal and the potential for hypertrophic scarring and postinflammatory pigmentary changes.[14]

Radiotherapy can be used in the treatment of NMSC either as a primary or an adjuvant therapy and can be an excellent treatment choice in a select patient population, including older patients who cannot tolerate extensive surgery, patients for whom surgery would be extremely disfiguring, and patients with aggressive SCC with perineural invasion or lymph node metastasis.[28] To minimize local tissue destruction, the radiation is typically delivered in fractionated doses, which allows healthy tissue time to recover between treatments. The main side effects of this treatment modality are dermatologic and include pruritus, alopecia, depigmentation, atrophy, and telangiectasias.

Photodynamic therapy (PDT) involves the application of either aminolevulinic acid (ALA) or methylaminolevulinate (MAL; Metvix, Galderma Pharma SA, Lausanne, Switzerland) to the skin.[29] After being preferentially absorbed by malignant cells in the epidermis, these two photosensitizers are converted to protoporphyrin IX in mitochondrial and lysosomal membranes. Subsequent irradiation with light of a wavelength between 450 and 750 nm excites protoporphyrin and results in the creation of reactive oxygen species, which induce apoptosis of the malignant cells. Currently, the use of MAL-PDT is indicated in the treatment of superficial BCC of any size outside the H zone of the face. Evidence indicates that treatment of deeper penetrating NMSC lesions is limited by the depth of penetration possible with PDT. Rhodes and colleagues achieved a 5-year cure rate of 76% with MAL-PDT of nodular BCC, with 87% of cases resulting in a good to excellent cosmetic outcome.[30] No significant difference in efficacy was noted in a study comparing ALA-PDT to cryotherapy for the treatment of superficial and nodular BCC.[31] Comparing MAL-PDT to 5-FU and cryotherapy in the treatment of SCC in situ, Morton and colleagues found that MAL-PDT resulted in lower recurrence rates than either of the other two treatment options.[32] The effectiveness and favorable cosmesis of PDT have resulted in high patient preference in clinical trials.[33]

A number of lasers have been explored in the treatment of NMSC. Carbon dioxide (CO_2) lasers (10,600 nm), which cause nonspecific tissue destruction through absorption by water in the epidermis, have been used successfully as a mono- or combination therapy in the treatment of NMSC.[25] Horlock and colleagues were able to completely ablate all superficial BCCs in one series using the CO_2 laser.[34] The authors further concluded that CO_2 laser treatment is up to three times faster than conventional excision, making it an ideal treatment option for a patient with multiple superficial BCCs. Combination with curettage provides a bloodless surgical field, leading to optimal vi-

sualization and minimal nonspecific thermal damage and scarring.[35]

Several recent reports have attempted to use vascular lasers in the treatment of NMSC. The pulsed dye laser (PDL) with a 585 to 595 nm wavelength works on the principle of selective photothermolysis of blood vessels, targeting hemoglobin in red blood cells within the vessels as a chromophore. Based on this principle, it was postulated that PDL would be effective in the treatment of BCC, given the reliance of these tumors on a specialized microvascular network, which results in the presence of telangiectasias.[35] With superficial and nodular BCCs ≤ 1.5 cm, Shah and colleagues achieved histologic clearance in 11 of 12 cases using a PDL.[36]

The long-pulsed alexandrite laser uses a wavelength of 755 nm and, like the PDL, has the capability to selectively target vasculature. It also has the added benefit of approximately twice the tissue penetration depth compared to the PDL.[37] For these reasons, Ibrahimi and colleagues decided to test the efficacy of the alexandrite laser in reducing the tumor burden of a patient with basal cell nevus syndrome with an extraordinary number of lesions (> 250 BCCs).[37] Of the 18 lesions treated, 15 maintained clinical clearance at the 2- and the 7-month follow-up using only a single pass, with histologic confirmation of clearance of 1 of the 15 cleared lesions at 7 months. When compared to a clearance rate of only 14% with the PDL when only one pass is used, and given the known benefit of deeper tissue penetration with the alexandrite laser, further investigation into its potential as an NMSC treatment modality is warranted.

Investigational Treatments

Several investigational treatments are currently in clinical trials that may represent exciting new treatment options for NMSC. For BCC, the forefront of investigational medical therapy largely centers on attempts to antagonize aberrant signaling of the Hh signaling pathway, which, as explained earlier, is a predominant feature of this tumor type. The most promising Hh inhibitor is GDC-0449, a small-molecule inhibitor of smoothened (Smo), an activating G protein–coupled receptor protein downstream of the *PATCHED1* receptor.[38] GDC-0449 has now entered phase II clinical trials after encouraging early results.[16] In fact, one patient with basal cell nevus syndrome treated with daily dosage of 270 mg of GDC-0449, who refused further surgical management after an enormous number of previous surgical excisions, had a nearly complete clearing of all BCCs (except one lesion) after 36 weeks. However, GDC-0449 does not come without side effects, the most significant of which have thus far been reported to be alopecia of the scalp, eyebrows, and eyelashes.

The strategy in the search for novel therapeutic options for SCC includes attempts to inhibit EGFR and vascular endothelial growth factor (VEGF) and its receptor, all of which have been shown to be overexpressed in a proportion of SCC tumors. Cetuximab is a monoclonal antibody against EGFR, and the literature contains some compelling evidence for its efficacy, particularly in the treatment of advanced or unresectable SCC. In one case, a 92-year-old male with unresectable lymph node SCC metastases from a previous head and neck SCC primary tumor was treated with cetuximab monotherapy, with the achievement of a complete response after 4 months of weekly treatment at a dose of 250 mg/m^2.[39] In another case, similarly impressive results were achieved when cetuximab was combined with the cyclooxygenase-2 inhibitor celecoxib.[40] A large study comparing radiotherapy alone to radiotherapy with weekly cetuximab infusions found statistically significant increases in the response rate, the duration of locoregional control, and overall survival.[41] The main side effects documented in studies so far include hypertrichosis and a papulopustular acneiform eruption, neither of which limits the duration or intensity of treatment.[16] Bevacizumab is a monoclonal antibody against VEGF and, due to promising early results, is currently in phase III trials for the treatment of recurrent and metastatic head and neck SCC.

Finally, further avenues of research are currently under way into the treatment of advanced SCC. Briefly, some of the therapies being investigated are inhibitors of the PI3K/AKT pathway, IGF-1R signaling, MET signaling, and tyrosine kinase inhibitors such as sorafenib and sunitinib.[42] With many of the corresponding drugs in phase II/III clinical trials, it seems to be only a matter of time before we enter a new era of targeted molecular therapy of SCC.

Conclusion

The incidence of NMSC is at unprecedented levels, after steady increases worldwide over the past several decades. Encouragingly, some recent Canadian studies have suggested that there may finally be some stabilization in incidence rates as a result of earlier detection and better prevention strategies. Although current treatment options,

which include both surgical and nonsurgical therapies such as topical agents, radiation, and ED + C, as well as newer therapies such as PDT and laser therapy, work well for a large majority of patients, recent advances in our understanding of NMSC molecular biology seem poised to usher in a new era of targeted molecular therapies, potentially allowing for the more effective management of advanced or challenging NMSC cases.

Acknowledgment

Financial disclosure of authors and reviewers: None reported.

References

1. Demers AA, Nugent Z, Mihalcioiu C, et al. Trends of nonmelanoma skin cancer from 1960 through 2000 in a Canadian population. J Am Acad Dermatol 2005;53:320–8.
2. Karagas MR, Greenberg ER, Spencer SK, et al. Increase in incidence rates of basal cell and squamous cell skin cancer in New Hampshire, USA. Int J Cancer 1999;81:555–9.
3. Donaldson MR, Coldiron BM. No end in sight: the skin cancer epidemic continues. Semin Cutan Med Surg 2011;30:3–5.
4. Rogers HW, Weinstock MA, Harris AR, et al. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. Arch Dermatol 2010;146:283–7.
5. Buettner PG, Raasch BA. Incidence rates of skin cancer in Townsville, Australia. Int J Cancer 1998;78:587–93.
6. de Vries E, van de Poll-Franse LV, Louwman WJ, et al. Predictions of skin cancer incidence in the Netherlands up to 2015. Br J Dermatol 2005;152:481–8.
7. Wassberg C, Thorn M, Johansson AM, et al. Increasing incidence rates of squamous cell carcinoma of the skin in Sweden. Acta Derm Venereol 2001;81:268–72.
8. Brewster DH, Bhatti LA, Inglis JH, et al. Recent trends in incidence of nonmelanoma skin cancers in the east of Scotland, 1992-2003. Br J Dermatol 2007;156:1295–300.
9. Hannuksela-Svahn A, Pukkala E, Karvonen J. Basal cell skin carcinoma and other nonmelanoma skin cancers in Finland from 1956 through 1995. Arch Dermatol 1999;135:781–6.
10. Madan V, Lear JT, Szeimies RM. Non-melanoma skin cancer. Lancet 2010;375:673–85.
11. Kricker A, Armstrong BK, English DR, et al. Pigmentary and cutaneous risk factors for non-melanocytic skin cancer—a case-control study. Int J Cancer 1991;48:650–62.
12. Patel RV, Frankel A, Goldenberg G. An update on nonmelanoma skin cancer. J Clin Aesthet Dermatol 2011;4:20–7.
13. Grossman D, Leffell DJ. Squamous cell carcinoma. In: Wolff K, Goldsmith LA, Katz SI, et al, editors. Fitzpatrick's dermatology in general medicine. 7th ed. New York: McGraw-Hill; 2008. p. 1028–35.
14. Carucci JA, Leffell DJ. Basal cell carcinoma. In: Wolff K, Goldsmith LA, Katz SI, et al, editors. Fitzpatrick's dermatology in general medicine. 7th ed. New York: McGraw-Hill; 2008. p. 1036–41.
15. So PL, Tang JY, Epstein EH. Novel investigational drugs for basal cell carcinoma. Expert Opin Investig Drugs 2010;19:1099–112.
16. O'Bryan KW, Ratner D. The role of targeted molecular inhibitors in the management of advanced nonmelanoma skin cancer. Semin Cutan Med Surg 2011;30:57–61.
17. Jung GW, Metelitsa AI, Dover DC, et al. Trends in incidence of nonmelanoma skin cancers in Alberta, Canada, 1988-2007. Br J Dermatol 2010;163:146–54.
18. Gallagher RP, Ma B, McLean DI, et al. Trends in basal cell carcinoma, squamous cell carcinoma, and melanoma of the skin from 1973 through 1987. J Am Acad Dermatol 1990;3:413–21.
19. Hayes RC, Leonfellner S, Pilgrim W, et al. Incidence of nonmelanoma skin cancer in New Brunswick, Canada, 1992 to 2001. J Cutan Med Surg 2007;11:45–52.
20. Stern RS. Prevalence of a history of skin cancer in 2007: results of an incidence-based model. Arch Dermatol 2010;146:279–82.
21. Mosterd K, Krekels GA, Nieman FH, et al. Surgical excision versus Mohs micrographic surgery for primary and recurrent basal-cell carcinoma of the face: a prospective randomized controlled trial with 5-years' follow-up. Lancet Oncol 2008;9:1149–56.
22. Rowe DE, Carroll RJ, Day CL. Mohs surgery is the treatment of choice for recurrent (previously treated) basal cell carcinoma. J Dermatol Surg Oncol 1989;15:424–31.
23. Perkins W. Who should have Mohs micrographic surgery? Curr Opin Otolaryngol Head Neck Surg 2010;18:283–9.
24. Love WE, Bernhard JD, Bordeaux JS. Topical imiquimod or fluorouracil therapy for basal and squamous cell carcinoma: a systematic review. Arch Dermatol 2009;145:1431–8.
25. Amini S, Viera MH, Valins W, et al. Nonsurgical innovations in the treatment of nonmelanoma skin cancer. J Clin Aesthetic Dermatol 2010;3:20–34.
26. Mohs FE, Jones DL, Bloom RF. Tendency of fluorouracil to conceal deep foci of invasive basal cell carcinoma. Arch Dermatol 1978;114:1021–2.
27. Spencer JM. Pilot study of imiquimod 5% cream as adjunctive therapy to curettage and electrodesiccation for nodular basal cell carcinoma. Dermatol Surg 2006;32:63–9.
28. Neville JA, Welch E, Leffell DJ. Management of nonmelanoma skin cancer in 2007. Nat Clin Pract Oncol 2007;4:462–9.
29. Brightman L, Warycha M, Anolik R, et al. Do lasers or topicals really work for nonmelanoma skin cancers? Semin Cutan Med Surg 2011;30:14–25.

30. Rhodes LE, de Rie MA, Leilsdottir R, et al. Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma. Arch Dermatol 2007;143:1131–6.
31. Wang I, Bendsoe N, Klinteberg CA, et al. Photodynamic therapy vs. cryosurgery of basal cell carcinomas: results of a phase III clinical trial. Br J Dermatol 2001;144:832–40.
32. Morton C, Horn M, Leman J, et al. Comparison of topical methyl aminolevulinate photodynamic therapy with cryotherapy or fluorouracil for treatment of squamous cell carcinoma in situ: results of a multicenter randomized trial. Arch Dermatol 2006;142:729–35.
33. Lehman P. Methyl aminolaevulinate-photodynamic therapy: a review of clinical trials in the treatment of acitinic keratoses and nonmelanoma skin cancer. Br J Dermatol 2007;156:793–801.
34. Horlock N, Grobbelaar AO, Gault DT. Can the carbon dioxide laser completely ablate basal cell carcinomas? A histological study. Br J Plast Surg 2000;53:286–93.
35. Choudhary S, Tang J, Elsaie ML, et al. Lasers in the treatment of nonmelanoma skin cancer. Dermatol Surg 2011;37:1–17.
36. Shah SM, Konnikov N, Duncan LM, et al. The effect of 595 nm pulsed dye laser on superficial and nodular basal cell carcinomas. Lasers Surg Med 2009;41:417–22.
37. Ibrahimi OA, Sakamoto FH, Tannous Z, et al. 755 nm alexandrite laser for the reduction of tumor burden in basal cell nevus syndrome. Lasers Surg Med 2011;43:68–71.
38. Goppner D, Leverkus M. Basal cell carcinoma: from the molecular understanding of the pathogenesis to targeted therapy of progressive disease. J Skin Cancer 2011. [Epub 2010 Dec 29]
39. Kim S, Eleff M, Nicolaou N. Cetuximab as primary treatment for cutaneous squamous cell carcinoma to the neck. Head Neck 2011;33:286–8.
40. Jalili A, Pinc A, Pieczkowski F, et al. Combination of an EGFR blocker and a COX-2 inhibitor for the treatment of advanced cutaneous squamous cell carcinoma. J Dtsch Dermatol Ges 2008;6:1066–9.
41. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354:567–78.
42. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010;11:21–8.