Author's response to reviews

Title: Case Report: Giant Perineal Keloids Treated with Post-Excisional Radiotherapy.

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Author's response to reviews: see over
To whom it may concern,

We greatly appreciate the opportunity to address the listed concerns of reviewer #1 and appreciate the acceptance recommendation of reviewer #2. Such a thorough attention to detail by the reviewer has resulted in an extended reply of nearly the length of the case report. As stated previously, this case report was not intended to serve as an exhaustive review. In order listed by the reviewer, I will address the noted Major Compulsory Revisions:

1. The confusing terms have been so removed.
2. While several authors have advocated the rescinding of the term “spontaneous keloid”, with the ideation echoed by the reviewer that it is unlikely that such keloids arose de novo without any underlying trauma. However, the patient noted no specific related perineal injury, wound or trauma. Additionally, it may be that the paucity of cases within the perineum may be due to the fact that it is rarely the object of incidental injury or minor trauma. It is, epistemologically, difficult for me to disprove the negative that no unrecollected trauma occurred; thus, “without recollection of any notable traumatic event”, “arising in the absence of an ascribed trauma”, “without recalled dermal injury or abrasion”, and “without apparent external cause” in lieu of the more parsimonious, but more questionable “spontaneous”. It should be added that this patient, who has had more than 10 keloids over her lifetime, describes the keloids as “just popping up from time to time”, and denied to the interviewing physician any temporal association with an injury in this specific case.
3. We utilized immediate radiotherapy, with the 1st treatment on the day following excision, as in the larger series of keloids by Sallstrom, Dinh, and Ragoowansi (see new Table 1). However, we are cognizant of the findings of Enhamre et al. (see new Table 1), who could discern no advantage to 3 vs. 14 days post-excision inception of radiation treatment, and thus see no particular dilemma in a modest delay (3-14 days) if necessary.
4. a. The patient’s newest recurrent lesions are, at least grossly, similar in coloration; however, the size is not as pronounced as the photographed lesions, and it exhibited a dome-like, as opposed to the more pedunculated perineal lesion. However, as alluded to in Bayat et al. (Br J Plast Surg. 2004 Mar; 57(2):122-33), such perineal keloids were quite rare, and, as yet, no compelling evidence exists to differentiate a therapeutic strategy predicated solely on gross morphologic appearance. Additionally, several series, such as Klumpar et al (J Am Acad Dermatol. 1994 Aug;31(2 Pt 1):225-31) do not note any effect of morphology or size on outcomes from post-excisional radiotherapy-treated keloids.
b. The reviewer wonders whether it is possible that her treated keloid may recur; in short, while post-radiotherapy is not unknown, it is markedly below many other established therapies. For convenience, I have added a small chart to the case report outlining a few notable extant series regarding recurrence rates for keloids post-radiotherapy; as I mentioned previously, this was not intended as an exhaustive effort, rather as an illustrative case report. Nonetheless, I hope I may me forgiven the extra references and space in order to clarify a bit.
Additionally, though only a single trial (Sclafani et al) was part of a prospective randomized series, historical control rates of 67-97% local control for approximately 1-year, and approximately 80% local control at 5-years are the current baselines for radiotherapy of keloids.

c. As to the query of how many times the authors will treat a comparatively young woman, the answer, is typically, as infrequently as possible; however, there are several cases noted in the literature where retreatment of previously irradiated keloids has been utilized to good result. Most recently, Garg et al (Radiotherapy and Oncology, Volume 73, Issue 2, Pages 233-236) report an 88% initial success rate in 17 patients treated for salvage of previously irradiated lesions.

5. The number of treatment session (or fractions) has yet to be optimally defined. One of the highest recurrent rates in an English-language series, Ogawa et al (see table) utilized single-fraction electrons; aside from this we feel several distinct fractionation schema seem equivalently effective, albeit based on the sparse extant series data. The main safety concern, as alluded to in the next item, would be the stochastic risk of secondary malignancies.

6. There is indeed a potential cost to utilization of radiotherapy. As noted above there is a stochastic risk of secondary malignancies proportional to the dose received. However, to date there have been minimal reported secondary malignancies in post-radiotherapy keloid patients. A case study and review by Botwood et al. (Br J Radiol. 1999 Dec;72(864):1222-4.) notes a case of a patient who received radiotherapy for a keloid and subsequently developed breast cancer, and collate case series with potentially attributable secondary malignancies with keloid radiotherapy, in contrast to quoted “0% carcinogenicity” in several series sets. Dinh et al (Australas J Dermatol. 2004 Aug;45(3):162-6) notes that in a cumulative review by Ragoowansi (Plast Reconstr Surg. 2003 May;111(6):1853-9.) five (5) possible secondary malignancies were noted in 6,741 treated keloids, for crude risk of 1/1,348 patients, according to the literature. In any effort to characterize the risk from keloid radiotherapy, one can approximate the risk to specific organs based on population-based models derived from exposure to the atomic bomb. Consequently, a dose of 22 Gy would give the patient an increase in stochastic risk of skin cancer of .0044 times that of an untreated patient. The proportional expected risk of subsequent malignancies, while quite low, does pose some risk, and should be discussed with every patient. However, recent data suggests that the rates of secondary malignancy may if act be lower than in atomic bomb survivors (Little MP Int J Radiat Biol. 2001 Apr;77(4):431-64). The following text was added “Additionally, there is a small, but notable stochastic risk for future secondary malignancy inherent in any radiation exposure. However, at present, few series have exhibited notable secondary carcinogenesis; Dinh et al.[10] note that in a cumulative review by Ragoowansi[11] five (5) possible secondary malignancies were noted in 6,741 treated keloids, for crude risk of 1/1,348 patients, according to the literature. Consequently, patients must be informed and radiotherapy used judiciously, and with careful follow-up of patients over the course of their lives.”

7. As the stochastic risk of secondary malignancy is not markedly higher than the general population, we follow-up with patients at 3-week, 3-, 6- and 12 month
intervals, and for 5 years annually thereafter. Afterwards, we suggest that the patient undergo standard screening for malignancies and continued follow-up with the primary dermatologic surgery or primary care team as indicated, noting the exceedingly small but real potential for carcinogenesis. The following text was added “Additionally, there is a small, but notable stochastic risk for future secondary malignancy inherent in any radiation exposure. However, at present, few series have exhibited notable secondary carcinogenesis; Dinh et al. (see new Table 1) note that in a cumulative review by Ragoowansi[11] five (5) possible secondary malignancies were noted in 6,741 treated keloids, for crude risk of 1/1,348 patients, according to the literature. Consequently, patients must be informed and radiotherapy used judiciously, and with careful follow-up of patients over the course of their lives.”

8. The absolute contraindications are for those of radiotherapy in general (i.e. pregnant patients); however, a relative contraindication is noted for children, as developmental effects as well as increased secondary cancer risks are possible. In our estimations, radiation therapy is an excellent option in patients for whom standard excision has failed, or who present with advanced and recurrent lesions, and should be considered in select cases for front-line therapy. The phrase “in adults” was added, as was additional text to the final paragraph.

We greatly appreciate the opportunity to reply to the auditor’s constructive comments, and await final recommendations regarding this report.

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