Dermatology Practical & Conceptual

Spontaneous Regression of Well-Differentiated Squamous Cell Skin Cancer Following Partial, Diagnostic Biopsy: Retrospective Cohort in Queensland

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Key words: Squamous Cancer, Spontaneous Resolution

Citation: Wilkinson D, Sottovia J, Hoogstad S. Spontaneous Regression of Well-Differentiated Squamous Cell Skin Cancer Following Partial, Diagnostic Biopsy: Retrospective Cohort in Queensland. *Dermatol Pract Concept*. 2025;15(4):5632. DOI: https://doi.org/10.5826/dpc.1504a5632

Accepted: June 26, 2025; **Published:** October 2025

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Well-differentiated squamous cell skin cancer (WDSCC) is common in sun-exposed populations. Guidelines promote active treatment, with excision preferred. Isolated cases of spontaneous regression (SR) have been reported. Having observed multiple patients with apparent SR following partial, diagnostic biopsy, we did a retrospective cohort study to explore this further.

Objectives: We sought to report frequency of SR of WDSCC following partial biopsy by a general practitioner (GP) in a primary care setting and referral to a public hospital general surgery service for excision, to report patient characteristics, and to estimate the time interval between biopsy and SR.

Methods: Retrospective cohort study (22 months) of patients in Queensland, Australia, with a diagnosis of WDSCC following a partial biopsy by a GP. SR was defined as no clinical or dermoscopy evidence of squamous cell carcinoma (SCC).

Results: Among 153 consecutive patients with WDSCC referred for excision, 51 showed SR at consultation (33.3%, 95% CI: 25.6–41). There was no significant difference in age or sex of the SR and

non-SR groups. In almost all patients with SR (N=49, 96.1%), lesions were located below the knee, compared with 90 (88.2%, *P*=0.042) without SR. Average interval between biopsy and surgical consultation was 13.6 weeks (range 2.7–24.7 weeks).

Conclusions: WDSCC may spontaneously resolve following partial, diagnostic biopsy more often than previously reported. These preliminary observations may have implications for treatment options, especially among frail patients with comorbidities.

Introduction

Squamous cell carcinoma (SCC) of the skin is the second most common type of skin cancer worldwide. It typically develops in sun-exposed parts of the body, particularly in older people with fair skin. The primary risk factor is cumulative ultraviolet (UV) radiation exposure. Other risk factors include chronic immunosuppression, previous radiation therapy, and chronic wounds. While SCC has a favorable prognosis when detected early, it has the potential for local invasion and metastasis, particularly in high-risk anatomical sites on head and neck. The global incidence is rising, due to ageing populations, increased sun exposure, and improved detection [1].

SCC represents a significant public health burden in Australia, with the highest rates of skin cancer in the world. Due to the combination of high UV exposure, predominantly fair-skinned population, and outdoor lifestyle, Australia's incidence rates of SCC are more than five times those seen in other Western countries, and Queensland reports the highest rates in Australia [2]. The economic impact is substantial, with skin cancers (including SCC) costing the Australian healthcare system over $1.5 billion annually. While mortality rates remain relatively low, the sheer volume of cases creates a significant burden on healthcare resources [3].

While actinic keratosis typically resolves spontaneously when UV exposure is reduced, and the natural history of keratoacanthoma (considered a form of SCC by many but not all) is characterized by spontaneous resolution, SCC does not resolve spontaneously [4]. We observed apparently spontaneous resolution among several patients referred to a general surgical service for SCC excision following partial, diagnostic biopsy by their general practitioner (GP). We therefore designed a retrospective cohort study to explore this further.

Objectives

1. To report the frequency of SR of WDSCC following partial, diagnostic biopsy by a general practitioner (GP) in a primary care setting and referral to a public hospital general surgery service for excision.
2. To report characteristics of patients showing SR, and compare these with patients not showing SR.
3. To estimate the time interval between biopsy and spontaneous resolution, using the interval between biopsy and surgical consultation (with patient reports) as a proxy.

Methods

We used the STROBE checklist [5].

Study Design

A retrospective cohort study was conducted over a 22-month period between December 2022 and September 2024.

Setting

Sunshine Coast Universityospital and Health Service (SCHHS), Sunshine Coast, Queensland, Australia. The health service serves approximately 500,000 people from the heavily populated coast, through more rural farming areas into remote, smaller settlements [6]. GPs typically biopsy suspicious skin lesions in their clinics using a punch biopsy technique (or less often, a shave biopsy). Most GPs then refer patients for treatment, depending on the size and location of the lesion, patient characteristics and comorbidities, and their own procedural skill level.

Referral guidelines are provided via HealthPathways [7]. and patients are referred for excision to either the General Surgery Service (lesions below the head and neck) or Plastic Surgery Service (lesions on the head and neck). All GP referrals are made centrally to the SCHHS and are reviewed and allocated to services and clinics there. The written referral (not the patient) is reviewed by a clinical nurse and a surgeon and allocated to the waiting list, according to urgency. WDSCC are usually considered non-urgent (category 3), with specialist consultation recommended within 365 days, or semi-urgent (consultation recommended within 90 days) [8].

Participants

Consecutive patients with a histological diagnosis of WDSCC following a partial, diagnostic biopsy of a suspicious

lesion, conducted by the patient's GP in a primary care at Maleny Hospital, part of the SCHHS. All other subtypes of SCC were excluded.

Variables

Age, sex, diagnosis, time interval between biopsy and surgical consultation, spontaneous resolution or not of the biopsied lesion.

Spontaneous resolution (SR) was defined as the absence of any clinical or dermatoscopic evidence of SCC and the presence of a flat scar clinically, with dermoscopy consistent with a scar.

Data Sources

All data were extracted from the patients' electronic medical record by DW and SH. Ethical approval was granted by Metro South Health Human Research Ethics Committee (HREC/2024/QMS/106985) on 2 September 2024.

Bias

This was minimized by including all consecutive patients with a diagnosis of WDSCC who attended this general surgery clinic.

Study Size

A total of 153 consecutive patients with a confirmed pathological diagnosis of WDSCC following partial, diagnostic biopsy of a suspicious lesion by the patient's GP.

Quantitative Variables

We report the number of patients with WDSCC, the number (%, and 95% confidence intervals [CI]) with SR, age and sex, and lesion location, comparing SR with non-SR patients and time interval between biopsy and surgical consultation.

Statistical Methods

Statistical analysis was performed using Microsoft Excel 2010. Descriptive statistics were used to summarize the data, with categorical variables expressed as frequencies and percentages. CI for proportions were calculated using the normal approximation method (SAS/STAT software, Version 9.4 (SAS Institute Inc., Cary, NC). Data visualization, including tables and figures, were generated using Excel charts to illustrate findings.

Results

Over the 22-month study period, 153 consecutive patients with biopsy-proven WDSCC were consulted at the general surgery clinic. Seven patients had more than one WDSCC, representing 160 lesions in all.

Of the 153 patients (with 160 lesions, Table 1), 51 patients (with 54 lesions) exhibited spontaneous resolution at the time of surgical consultation, corresponding to 33.3% (95% CI: 25.6–41) of patients and 35.3% (95% CI: 27.7%–42.9) of lesions. Mean and standard deviation (SD) of the age of the SR group was not statistically significantly different from the non-SR group: 73.7 (8.5) years vs 75.2 (6.3) (P=0.18). In almost all patients (N=49, 96.1%) with SR, lesions (N=51, 94%) were mainly located below the knee; in non-SR patients the proportion below the knee was 90/102 (88.2%, P=0.042). Average interval between biopsy and surgical consultation was 13.6 weeks (range 2.7–24.7 weeks), with no difference between SR and non-SR groups (Figure 1).

Discussion

These preliminary observations suggest that WDSCC may have relatively high rates of spontaneous resolution following a partial diagnostic biopsy over a period of a few weeks. Our findings suggest that this may occur in approximately

Table 1. Characteristics of SR and non-SR Groups.

	SR	Non-SR
Number of patients (%)	51 (33.3)	102 (66.7)
Number of lesions (%)	54 (33.8)	106 (66.2)
Age at point of biopsy years, mean (SD)	73.7 (8.5)	75.2 (6.3)
Sex, number of patients (%)		
Male	29 (56.9)	58 (56.9)
Female	22 (43.1)	44 (43.1)
Location, Number of lesions (%)		
Lower leg (below the knee)	49 (94.4)	90 (88.2)
Forearm	2 (5.6)	12 (11.8)

Abbreviations: SR: spontaneous regression.

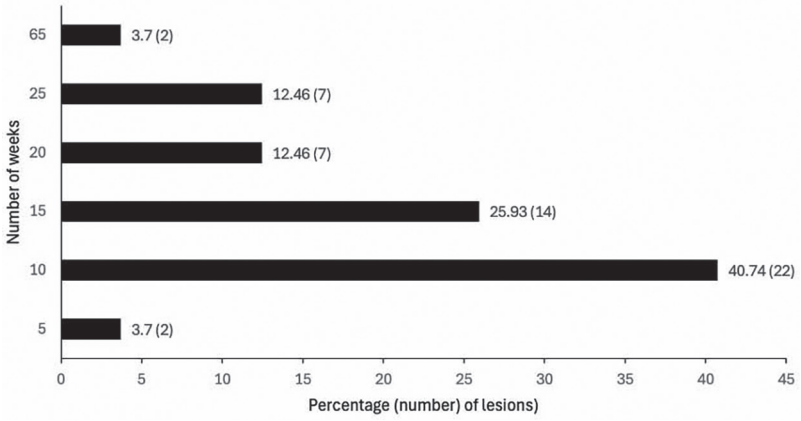

Figure 1. Distribution of time interval between biopsy and surgical consultation.

one third of patients, noting that our retrospective cohort was restricted largely to patients with lesions below the head and neck. Most patients with spontaneous resolution (SR) had lesions on the lower leg below the knee, and at a higher proportion than those without SR. There was no significant difference in age or sex between the two groups.

Caution needs to be applied when estimating the time taken for SR to occur. The data we have were for the interval between biopsy and surgical consultation. Spontaneous resolution inevitably occurred prior to the consultation, so the time to SR was shorter than the time to consultation. Most patients with SR reported that the biopsy took 1–2 weeks to heal and that the lesion itself then slowly and steadily disappeared over the next 3–4 weeks. Several patients with SR started their consultation with us by saying, "I think I am wasting your time; the cancer seems to have gone." Ideally, future studies will carefully monitor lesions following biopsy to determine the precise timelines for healing and any SR (or not) over perhaps a 2- to 3-month period.

Spontaneous resolution of SCC, without any procedure, is very rare [9], while rapid evolution and subsequent resolution of keratoacanthoma (widely regarded as a type of SCC is the norm [10] and resolution of actinic keratosis (a precursor of SCC) is also typical [11]. Furthermore, multiple case reports exist of spontaneous resolution of other cancers [12,13]. It is also well documented that in basal and squamous cancers that are incompletely excised, many (40% of SCC and 20% of BCC in one study [14]) show no residual tumor on re-excision, implying that some form of immune response as part of wound healing often leads to eradication of the tumor.

Our search of the literature did not find any report of studies like ours that explored rates of spontaneous resolution following partial, diagnostic biopsy.

These findings are preliminary, and some limitations do apply. This was a single site study, and while there was no selection bias in patients selected for surgical consultation at this clinic, it will be essential to replicate the study in other clinics and settings. It is important to affirm that all referrals to the public hospital service from all GPs across this large population are sent to a single central site at the university hospital for review, triage, and surgical outpatient clinic allocation. Our study was made possible by the inherent timelines that occur when a GP refers a patient with WDSCC to this public hospital general surgery service, where the referral is reviewed, triaged, and allocated to a general surgical outpatient clinic for consultation (and then surgical intervention, as required). This process typically takes a few weeks, and when patients are allocated as category 2 or 3, as is typical for WDSCC, these timelines can easily become a few months [8]. These realities allowed us to explore the rates and timelines of spontaneous resolution following partial, diagnostic biopsy.

It is important to stress that the procedure done by the GP was in almost all cases a punch biopsy (usually a 3 mm punch), and only occasionally a shave biopsy. In all cases the biopsy was partial (with peripheral margins involved) and diagnostic and was not an excisional biopsy. We do not have data on original lesion size as this was usually not recorded by the GP in the referral. Any further studies should be designed to include this information, and it would be useful to estimate what proportion of the lesion is removed by a diagnostic, partial biopsy.

The diagnosis of WDSCC was provided by the pathology report presented to the patient's GP. GPs choose their preferred private pathology service in Queensland, and most specimens were reported by the four major pathology providers in the area. The literature recognizes some variation in accuracy of reporting of WDSCC and other skin cancers [15]. We were limited, in this preliminary study, to the pathology reports provided to the GP and included in the referral. Future studies could usefully include standardized reporting, either from a single dermatopathologist or with blinded review of at least a sample

of slides to provide greater confidence in diagnostic accuracy. It is possible, for example, that some of the lesions in our study exhibited features of keratoacanthoma but were not reported as such, and hence were more likely to spontaneously resolve. It would be appropriate to capture immunosuppression status also.

Conclusion

If these findings are confirmed and extended, what are the possible implications? We work in a setting with very high levels of skin cancer, and large numbers of older patients (often with comorbidities) present with WDSCC on the lower leg, often repeatedly. Treatment can be challenging, as although typically clinically indolent, guidelines do recommend active treatment usually by surgical excision or other destructive means [16]. Furthermore, diagnosis is essential, and most patients do want these often ugly and irritating lesions treated. However, treatment-fatigue among patients with multiple recurrent lesions is common. Surgical excision below the knee is often challenging due to poor skin quality, tight skin, and restricted arterial circulation [17]. Flaps or grafts are often needed, with healing not assured, and poor healing with chronic ulceration is not uncommon and can be very debilitating.

A period of close clinical observation following diagnostic biopsy could be appropriate in selected patients. If gradual spontaneous resolution is observed and complete healing is documented, patients could then be followed carefully with regular skin examinations and review. Such an approach has been advocated for selected cases of low-risk basal cell cancer [19]. A similar approach is also adopted for lower risk cases of prostate cancer, with active surveillance preferred to immediate intervention [19].

Our study provides novel insights into the natural history of WDSCC following a partial, diagnostic biopsy and adds to the literature reporting resolution of incompletely excised SCC and BCC as well as to the literature on spontaneous resolution of other cancers. Further studies to clarify, confirm, and expand on our observations are warranted.

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