INVESTIGATIVE REPORT

Comparative Analyses of Tumour Volume Doubling Times for Periocular and Non-periocular Head and Neck Basal Cell Carcinomas

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Basal cell carcinomas are the commonest solid malignancy in humans and thought to grow faster in the periocular region. We measured growth rates between periocular and non-periocular nodular basal cell carcinomas in the head and neck region from high-resolution digital photos and operative notes. The non-periocular basal cell carcinomas (head and neck) showed a mean tumour volume doubling time of 129.8±21.74 ($n=79$) days, and the periocular basal cell carcinoma a mean of 177.5±37.21 ($n=47$) days. The unpaired *t*-test with Welch correction showed that this difference was not significant ($p=0.2719$). The mean tumour volume doubling time was 147.59±37.75 days for head and neck basal cell carcinomas overall. For the first time, tumour volume doubling times for nodular basal cell carcinomas in the periocular versus non-periocular regions for the head and neck area were analysed, with no significant differences demonstrated. Further, comparison of basal cell carcinoma growth rates with other common solid tumours confirmed that basal cell carcinomas are slow growing malignancies.

Key words: periocular; non-periocular head and neck basal cell carcinoma; BCCs; tumour volume doubling time; growth rates.

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SIGNIFICANCE

Basal cell carcinomas are very common skin tumours which are locally destructive. It was thought that basal cell carcinomas around the eyes grow faster than those elsewhere based on one previous paper. We demonstrate that there is no evidence for this and also calculate tumour growth rates to show the position of basal cell carcinomas in a growth rate figure, compared to more malignant tumours. Our new data can guide clinicians as to how much time there is available for removal or treatment before crucial parts of our anatomy could be affected.

Basal cell carcinomas (BCCs) are the most common malignant tumour in humans, especially among fair skinned humans in the developed world (1–4). Indeed the prevalence rate of BCCs far surpasses all other malignancies (1–3) but since mortality from BCCs is very rare, it has long been considered more of an inconvenient nuisance, and most countries do not include them in their cancer registries.

Despite the rapidly increasing incidence rates being reported and the increasing burden on healthcare systems, BCCs have not been extensively researched and the amassed knowledge about the natural history of this common tumour is patchy at best.

In this study, we have tested the hypotheses that there are no significant differences between the growth rates of periocular nodular BCCs compared to other head and neck BCCs, and also derived tumour volume doubling times (TVDT) for comparison with those of other malignancies. Only BCCs of the nodular histological subtype were selected as it is likely that other subtypes such as the morphoeic, infiltrative or micronodular subtypes would not be visually well represented on the skin surface for measurement, plus these other subtypes of BCC may grow in a more diffuse or tendril-like pattern rather than a generally spherical pattern. Whether these other types of BCC are biologically distinct or have different growth rates is not known. BCCs have long been classified among the slower growing solid tumours of the skin (non-melanoma skin cancers) in contrast to the highly malignant skin tumours such as melanoma or Merkel cell carcinoma.

MATERIALS AND METHODS

A retrospective cohort study to study growth rates in BCCs in the periocular region (upper and lower eyelids, within the nasojugal fold, medial/lateral canthi) and non-periocular BCCs (defined as all other regions of the head and neck). The patient cohort was defined as those individuals who underwent Mohs micrographic surgery (MMS) between 1st January 2016 and 31st January 2018. Inclusion/exclusion criteria are detailed in **Table I**.

Nodular BCCs selected for the study, using the above criteria, allows narrowing and focus of the study on clinically very similar lesions. This is to decrease the expected biological variation found amongst different types of BCCs, and consequently their growth rates as well.

The patient details were retrieved from our hospital electronic patient record system and clinical image record. We were able to utilise the unique search parameters of the electronic database and hospital administration system to find patients with BCCs from 2016 onwards.

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Table I. Inclusion and exclusion criteria

Inclusion criteria
• Primary basal cell carcinoma
• Lesion treated with Mohs micrographic surgery
• Nodular histological subtype on Mohs surgery debulk specimen
• Localised to head and neck only
• Pre-treatment photographs with appropriate scale present
• Minimum of 14 days between initial assessment (photograph) and surgery
• Measurement of lesion recorded in Mohs operation note
Exclusion criteria
• Mixed histological subtypes on Mohs surgery debulk specimen
• Photographs where scale is not parallel to lesional skin surface
• Uncertainty about delineation of lesion border due to inadequate image quality on photograph
• Sharp debulking prior to initial Mohs layer performed with scalpel of entirety of clinically visible tumour which is then sent for conventional histological sectioning and analysis

Photographs of lesions were captured by the hospital clinical photography department following standardised local protocols (5) with a Nikon D800 full frame DSLR (Digital Single Lens Reflex) camera with a 105 mm macro lens with a fixed focal length. Lesions were photographed perpendicular to the skin surface at a 1:1 reproduction ratio with a F-stop of 25. This gives a depth of field of approximately 1 mm. Digital scales included in images were constructed in Adobe Photoshop by photographing a ruler at the same reproduction ratio. These are used instead of physical rulers as our experience suggests that these are equal if not superior to physical rulers (6) particularly in difficult to reach anatomic locations and hair bearing areas.

Final lesion sizes were obtained from the Mohs operation notes. Initial lesion sizes were measured on digital photographs taken at the outpatient clinic assessment of the patients by a single observer (AK) using the digital scale included with the image. Lesions were measured across their largest single dimension, *d*. Tumours were assumed to be spherical and their volume was calculated according to the following formula: $\text{Volume} = \frac{4}{3}\pi \left(\frac{2}{d}\right)^3$ (**Fig. 1**).

Growth rates of solid tumours can be easily estimated along the linear section of the Gompertzian growth curve (7–10). Visible and detectable tumours usually contain between 10^6 to 10^9 cells. Multiple examples of different solid tumours have demonstrated linearity of growth on a logarithmic scale during the early detectable phase (11–14).

Doubling times can be calculated from 2 observed time points, simply using the following equations:

$$\text{Ratio of change in volume, } R = \frac{\text{Volume at time of surgery}}{\text{Volume at initial assessment}}$$

$$\text{Number of doublings, } D = \log_2 R$$

$$\text{Doubling time in days, } DT = \frac{\text{Time between assessment and surgery (Days)}}{D}$$

A selection of histological specimens were examined and the diameter of individual BCC cells was measured a micrometer.

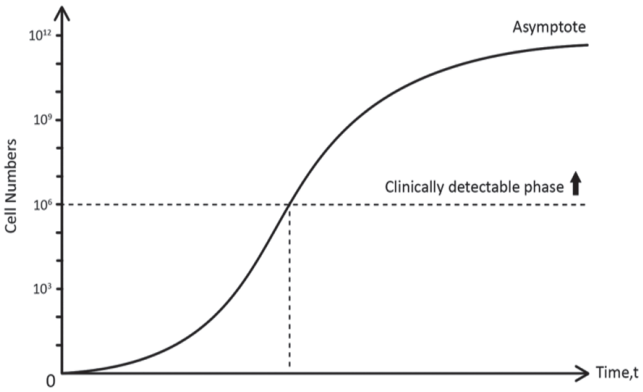

Fig. 1. Gompertzian Tumour Growth Curve.

Assuming these cells are spherical, an estimated volume of a BCC cell and the number of cells for a tumour of a given diameter can be derived from the following equations:

$$\text{Cell volume, } V_c = \frac{4}{3}\pi \left(\frac{\text{Cell diameter}}{2}\right)^3$$

$$\text{Tumour volume, } V_t = \frac{4}{3}\pi \left(\frac{\text{Tumour diameter}}{2}\right)^3$$

$$\text{Cells in tumour, } N_t = \frac{V_t}{V_c}$$

A further equation can then be used to estimate the age of the tumour assuming a single precursor cell.

$$\text{Age of tumour in days, } T_d = N_t \times DT$$

RESULTS

Table II shows the patient demographics and lesion characteristics. Continuous variables are expressed as mean ± standard deviation (SD). **Table III** shows actual sites of lesions. **Fig. 2** shows the doubling times for both periocular and non-periocular head and neck BCCs.

Using the unpaired *t*-test with Welch correction, the non-periocular head and neck BCCs have a mean TVDT of 129.8 days (SEM ±21.74 days) ($n=79$), and the periocular BCC have a mean of 177.5 days (SEM ±37.21 days) ($n=47$). The median values are 111.8 and 129.5 days respectively. The 2 tailed *p*-value is 0.2719 (non-significant). There is therefore no evidence to suggest that periocular BCCs grow faster than other head and neck BCCs (non-periocular BCCs) although the sample size is small. Indeed the trend is the converse, that the non-periocular BCCs may actually grow faster, although this is not significant.

However, total overall mean doubling time can be assumed to be accurately reflect the true overall mean, which is 147.59 days (SEM ±19.47). The SD is 218.6 days for the total cohort of head and neck (periocular and non-periocular) BCCs.

Fig. 3 shows the estimated position of BCC growth rates in comparison to other solid tumours. Data extracted for analyses from Friberg & Mattson 1997 (12).

The measured diameters of BCC cells histologically range from 2.5 to 10 microns. Assuming the minimum diameter of a clinically detectable tumour is 1 mm, this gives us a detection threshold of approximately 1 to 60 ($\times 10^6$) cells and an estimated tumour age of approximately 8–11 years. [These calculations are based on cellular size and volume only].

Table IV shows the number of cells in a tumour of a given diameter and the estimated tumour age ranges for tumour cells sized between 2.5–10 microns.

Table II. Patient demographics and lesion characteristics

	Head and neck lesion	Periocular lesion
Age, years, mean ± SD	69.1 ± 11.3	68.9 ± 14.6
Male:Female, *n*	38:41	25:22
Initial size, mm, mean ± SD	7.32 ± 3.48	7.23 ± 3.45
Initial volume, mm^3, mean ± SD	15.32 ± 7.28	15.15 ± 7.23
Size at time of surgery, mm, mean ± SD	9.77 ± 4.88	8.79 ± 4.62
Volume at time of surgery, mm^3, mean ± SD	20.47 ± 10.22	18.40 ± 9.67
Time to treatment, days, mean ± SD	84.2 ± 61.9	90.2 ± 59.36

Table III. Actual sites of lesions

	n
Head and neck	
Nose	46
Cheek	12
Lip	6
Forehead	4
Scalp	3
Temple	2
Ear	2
Preauricular	2
Brow	2
Periocular	
Medial canthus	25
Eyelid	17
Lateral canthus	5
Grand Total	126

There are significant overlaps between the ranges seen above and this illustrates the wide individual variation seen in BCCs in terms of size of cells, and does not allow for necrosis within tumour bodies, non-basal cellular components, connective tissue, etc.

Our data confirm that BCC growth rates can be considered slow growing compared to other malignant solid tumours. The fact that BCC are essentially non-metastasising solid tumours is almost undoubtedly the reason for the negligible mortality associated with this tumour as it means that the tumour can be removed *en bloc* or destroyed in the vast majority of cases without damage to vital internal organs that would threaten life.

DISCUSSION

TVDT have implications for patients ranging from specific life-affecting (screening programmes, prognosis, estimation of lifespan, etc.) to the legal and mundane (actuarial/risk estimations by insurance companies, court cases estimating when the primary or metastatic tumours arose, etc.).

BCCs have long had the reputation of being a slow growing and indolent tumour in humans, despite being

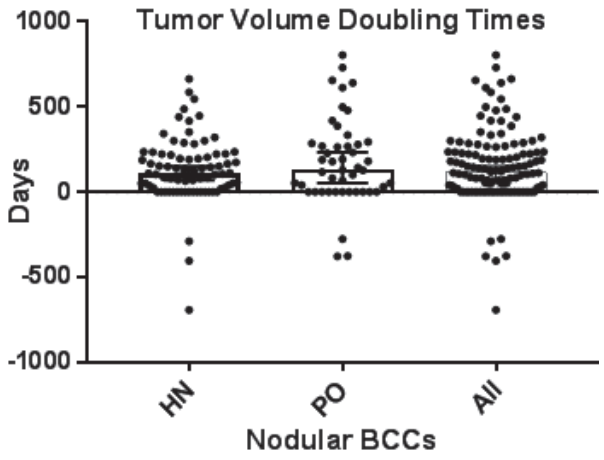

Fig. 2. Tumour volume doubling times for nodular basal cell carcinomas (periocular (PO) vs head & neck (HN) (non-periocular).

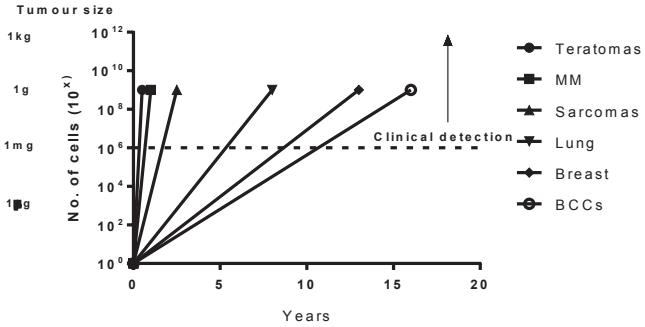

Fig. 3. Growth rates (estimated) for different solid tumours in comparison to nodular basal cell carcinomas (BCCs).

the most frequent malignancy by far (1, 2). This is due to the fact that directly attributable mortality to BCCs is extremely rare, and most developed countries do not even include this tumor in their cancer registries.

In contrast, BCCs incidence rates are rising rapidly, in conjunction with other non-melanoma skin cancer (NMSC) such as squamous cell carcinomas, Merkel cell carcinoma and eccrine porocarcinoma (1, 15–17). The cost and burden to the UK taxpayer is also rising rapidly and NMSC costs have been estimated to reach almost half a billion pounds in 2025 for the NHS (1).

Tan et al. (18) published observational data that suggested that periocular BCCs could grow rapidly, especially recurrent tumours, larger tumours and tumours in men. There was no direct comparison of growth rates between periocular and non-periocular tumours or other control groups. In this study, we wanted to examine whether there was evidence that BCCs actually grew at different rates based on their anatomical site of origin on the skin, calculate proper TVDTs to allow comparison with other tumours, and to estimate the BCC position in the hierarchy of human cancer growth rates for the first time.

We show that BCCs from periocular sites do not demonstrate faster growth rates than other non-periocular head and neck BCCs, indeed the converse may be true as the data trend is for a faster growth rate seen for the non-periocular tumours (non-significant). However, the sample size of 126 samples is not large and does not give sufficient analytical power for small differences. For the first time, we are able to estimate the TVDT for BCCs and give an approximation of the tumour's growth rate compared to other published data. We show that the mean

Table IV. Number of cells in a tumour of a given diameter and the estimated tumour age ranges for tumour cells sized between 2.5–10 microns

Tumour diameter	Number of cells	Time, days	Time, years
1 mm	$1x10^6$–$6x10^7$	2,942–3,827	8.1–10.5
2 mm	$8x10^6$–$5x10^8$	3,384–4,270	9.3–11.7
3 mm	$3x10^7$–$2x10^9$	3,643–4,529	10.0–12.4
4 mm	$6x10^7$–$4x10^9$	3,827–4,713	10.5–12.9
5 mm	$1x10^8$–$8x10^9$	3,970–4,855	10.9–13.3
6 mm	$2x10^8$–$1x10^{10}$	4,086–4,972	11.2–13.6
7 mm	$3x10^8$–$2x10^{10}$	4,185–5,070	11.5–13.9

TVDT for head and neck BCCs is approximately 150 days. There are no data for BCCs from non-periocular head and neck sites, therefore we cannot comment on whether those tumours grow faster or slower than the periocular head and neck ones. The wide SD from the sample seen above (218.6 days) demonstrates the wide biological variation in growth rates and even regression seen in some of these tumours in this cohort. This is consistent with the observed clinical characteristics for these BCCs, with some regressing or disappearing after punch biopsies, etc, and this phenomenon has been reported before (18).

BCCs do seem to grow slower than more malignant tumours, such as primary breast or colorectal tumours, but the insignificant mortality rate can almost certainly be attributed to their unique biological characteristic of not metastasising to distant sites. In spite of this, neglected BCCs can cause significant morbidity if present on functionally and cosmetically sensitive areas (T-zone of face) on or adjacent to structures such as the eyes and nose. A gradual, relentless tumour expansion leads to local invasion and destruction of these structures leading to disfigurement, blindness and loss of function. These locally advanced tumours are often impossible to resect completely as the deep margins are frequently involved and the resulting defect would lead to even worse morbidity. Early resection of BCCs in these areas, preferably with Mohs surgery, is therefore important. Recent developments in medical treatment such as the hedgehog signalling pathway inhibitors (vismodegib and sonidegib) (19) have offered new hope for reducing BCC tissue mass in the long-term (not available in the UK on the NHS, but available in other countries), or prior to salvage surgery.

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The authors have no conflict of interest to declare.

REFERENCES

1. Goon PKC, Greenberg DC, Igali L, Levell NJ. Predicted cases of U.K. skin squamous cell carcinoma and basal cell carcinoma in 2020 and 2025: horizon planning for National Health Service dermatology and dermatopathology. Br J Dermatol 2017; 176: 1351–1353.
2. Holm AS, Nissen CV, Wulf HC. Basal cell carcinoma is as common as the sum of all other cancers: implications for treatment capacity. Acta Derm Venereol 2016; 96: 505–509.
3. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol 2012; 166: 1069–1080.
4. Lucas R MT, Smith W, Armstrong B. Solar Ultraviolet Radiation: Global Burden of Disease from Solar Ultraviolet Radiation. Geneva: WHO; 2006.
5. Murdoch J. Standardization in clinical photography at Addenbrooke's Hospital. J Vis Commun Med 2005; 28: 68–71.
6. Bartley M. Photographic measuring scales. J Vis Commun Med 2012; 35: 152–154.
7. Dethlefsen LA, Prewitt JM, Mendelsohn ML. Analysis of tumor growth curves. J Natl Cancer Inst 1968; 40: 389–405.
8. Gompertz B. On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. Phil Trans Roy Soc London 1825; 115: 513–583.
9. Steel GG, Lamerton LF. The growth rate of human tumours. Br J Cancer 1966; 20: 74–86.
10. Winsor CP. The Gompertz Curve as a Growth Curve. Proc Natl Acad Sci USA 1932; 18: 1–8.
11. Collins VP, Loeffler RK, Tivey H. Observations on growth rates of human tumors. Am J Roentgenol Radium Ther Nucl Med 1956; 76: 988–1000.
12. Friberg S, Mattson S. On the growth rates of human malignant tumors: implications for medical decision making. J Surg Oncol 1997; 65: 284–297.
13. Spratt JS, Jr., Spratt TL. Rates of growth of pulmonary metastases and host survival. Ann Surg 1964; 159: 161–171.
14. Schwartz M. A biomathematical approach to clinical tumor growth. Cancer 1961; 14: 1272–1294.
15. Goon PK, Greenberg DC, Igali L, Levell NJ. Merkel cell carcinoma: rising incidence in the East of England. J Eur Acad Dermatol Venereol 2016; 30: 2052–2055.
16. Goon PK, Greenberg DC, Igali L, Levell NJ. Squamous cell carcinoma of the skin has more than doubled over the last decade in the UK. Acta Derm Venereol 2016; 96: 820–821.
17. Goon PKC, Gurung P, Levell NJ, Subramanian P, Yong ASW, Lee KYC, et al. Eccrine porocarcinoma of the skin is rising in incidence in the east of England. Acta Derm Venereol 2018; 98: 991–992.
18. Tan E, Lin FP, Sheck LH, Salmon PJ, Ng SG. Growth of periocular basal cell carcinomas. Br J Dermatol 2015; 172: 1002–1007.
19. Khoo AB, Ali FR, Lear JT. Defining locally advanced basal cell carcinoma and integrating smoothened inhibitors into clinical practice. Curr Opin Oncol 2016; 28: 180–184.