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Research letter

The aggressive behaviour of squamous cell carcinoma in epidermolysis bullosa: analysis of clinical outcomes and tumour characteristics in the Dutch EB Registry

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DEAR EDITOR, Epidermolysis bullosa (EB) is a group of rare heterogeneous genetic disorders characterized by mucocutaneous fragility with subsequent blisters and wounds.¹ Depending on the level of blister formation, EB is classified into four main types: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB) and Kindler EB (KEB). These main types are further divided into subtypes based on inheritance, molecular features and clinical characteristics.¹ In some forms of EB, patients have an increased risk of developing cutaneous squamous cell carcinoma (cSCC).^{2–7} Especially in the severe recessive subtype of DEB (RDEB-severe), cSCCs behave aggressively and are the leading cause of morbidity and death.^{3–7}

The pathogenesis underlying the increased risk of the development and the aggressiveness of EB-cSCCs is not fully understood. Although more data about the epidemiology of EB-cSCCs are available than about the pathogenesis, only a limited number of studies have been published about patients with EB-cSCCs captured in national EB registries.^{2,3,6,7} Information on clinical and tumour characteristics from a well-characterized EB registry can provide more insight into the development of EB-cSCCs, contributing to further research and facilitating high-quality care. The University Medical Center Groningen, Center for Blistering Diseases is the national expertise centre for EB in the Netherlands, and patients have been registered in the Dutch EB Registry since 1988. Here we present detailed data on the epidemiology, tumour characteristics and clinical outcomes of patients with EB-cSCCs collected over a 32-year period.

In this retrospective observational study, all patients with EB-cSCCs registered in the Dutch EB Registry from 1 January 1988 to 30 October 2020 were included. The diagnosis of EB had to be molecularly confirmed by mutation analysis, immunofluorescence and/or transmission electron microscopy, and the diagnosis of the cSCCs had to be proven by pathological analysis. Patient data were gathered from medical records, and descriptive statistical analysis was performed using SPSS version 27.0 (IBM, Armonk, NY, USA). The Local Ethics Review Board Pathology non-WMO studies approved the study. Data that support the findings of this study, including additional methods and results, are available upon direct request.

In the Dutch EB Registry, 22 of 578 patients with EB developed 78 cSCCs, with the highest frequency (nine of 34, 26%) in RDEB-severe, followed by KEB (one of five, 20%), JEB-intermediate (seven of 41, 17%) and JEB-localized (two of 15, 13%).

In RDEB-severe the median age at cSCC onset was the lowest, at 27.7 years (range 14.3–42.2). Half of the patients with EB-cSCCs developed metastases (11 of 22) and all 11 patients died eventually due to this metastatic disease. Most metastatic tumours occurred in RDEB-severe, with seven affected patients (seven of nine, 78%), followed by JEB-intermediate (three of seven, 43%). In RDEB-severe the median age at death of 37.5 years (range 22.8–43.3) was the lowest among all subtypes, whereas the median age at death of all other subtypes was above 57.3 years. The median survival after the first cSCC was 41 months in RDEB-severe (range 9–199), compared with 228 months in JEB-intermediate (range 22–302).

Fifty-three tumours were primary cSCCs (68%), while the remaining tumours were locally recurrent cSCCs (16 of 78, 21%) or not specified (nine of 78, 12%). Most primary cSCCs developed on the extremities (47 of 53, 89%) and the majority of all cSCCs (58 of 78, 74%) arose in areas of chronic wounds without a distinct clinical presentation. Overall, 63% of the invasive cSCCs had a tumour diameter of ≥ 2 cm (47 of 75), but they did not show other clinical or histopathological risk factors for the development of metastasis and local recurrences, including poor differentiation, and perineural or lymphovascular invasion (Table 1).

Due to the retrospective nature of the study and the relatively small sample size only descriptive statistics could be implemented. Nevertheless, this study shows that cSCC is a life-threatening complication not only in RDEB-severe but also in JEB-intermediate, demonstrated by an increased risk of metastasis and disease-specific death in both subtypes. Similarly to other EB cohorts, in patients with RDEB-severe, death occurred at a relatively young age with a short median survival after cSCC onset.^{6,7} Furthermore, this study presents the first thorough analysis of clinical and histopathological prognostic factors in EB-cSCCs, showing that these tumours possess an aggressive nature despite the absence of most high-risk factors. The only exception is the large tumour size, which was also reported in previous studies.^{4,5} However, it is questionable whether these factors are applicable for risk assessment in patients with EB, as their prognostic value is solely based on research performed in ultraviolet-induced cSCCs of people without EB.⁸

Table 1 Clinical outcomes and tumour characteristics of cutaneous squamous cell carcinoma (cSCC) in patients with epidermolysis bullosa (EB) in the Dutch EB Registry (1988–2020)

	Total	REBS	JEB-loc	JEB-int	RDEB-int	RDEB-sev	RDEB-inv	KEB
Patients with EB-cSCC/patients with EB in the registry (%)	22/578 (3.8)	1/8 (13)	2/15 (13)	7/41 (17)	1/23 (4)	9/34 (26)	1/11 (9)	1/5 (20)
Mutated genes in the patients with EB-cSCC ^a		KRT14	LAMA3, LAMB3, COL17A1, ITGB4		COL7A1	COL7A1	COL7A1	FERMT1
Age at cSCC onset (years), median (range) ^{b,c}	42.2 (14.3–81.9)	81.9	52.9 (49.0–56.8)	61.0 (28.0–72.2)	33.2	27.7 (14.3–42.2)	57.2	59.2
Metastasis	11 (50)	1 (100)	–	3 (43)	–	7 (78)	–	–
Deceased	17 (77)	1 (100)	–	6 (86)	–	8 (89)	1 (100)	1 (100)
Survival time (months), median (range) ^d	41 (2–302)	7	–	228 (22–302)	–	41 (9–199)	2	103
Cause of death: metastatic cSCC	11 (65)	1 (100)	–	3 (50)	–	7 (88)	–	–
Total number of cSCCs ^e	78	1	6	16	2	51	1	1
Primary cSCC	53 (68)	1 (100)	5 (83)	9 (56)	2 (100)	34 (67)	1 (100)	1 (100)
Recurrent cSCC	16 (21)	–	1 (17)	3 (19)	–	12 (24)	–	–
Location of primary cSCCs: extremities	47 (89)	1 (100)	3 (60)	9 (100)	2 (100)	31 (91)	–	1 (100)
Number of invasive cSCCs	75 (96)	1 (100)	6 (100)	15 (94)	2 (100)	49 (96)	1 (100)	1 (100)
Tumour diameter: < 2 cm ^f	11 (15)	–	1 (17)	1 (17)	–	7 (14)	1 (100)	1 (100)
Tumour diameter: ≥ 2cm	47 (63)	1 (100)	3 (50)	7 (47)	2 (100)	34 (69)	–	–
Histologically well differentiated ^g	41 (55)	–	4 (67)	6 (40)	1 (50)	28 (57)	1 (100)	1 (100)
Histologically moderately differentiated	18 (24)	1 (100)	–	3 (20)	1 (50)	13 (27)	–	–
Histologically poorly differentiated	6 (8)	–	–	2 (13)	–	4 (8)	–	–
Depth of invasion: ≤ 6 mm ^h	44 (59)	1 (100)	3 (50)	6 (40)	1 (50)	31 (63)	1 (100)	1 (100)
Depth of invasion: > 6 mm/invasion beyond SC fat	14 (19)	–	–	1 (7)	1 (50)	11 (24)	–	–
Perineural or lymphovascular invasion	1 (1)	–	–	–	–	1 (2)	–	–

The data are presented as n (%) unless stated otherwise. JEB-loc, junctional EB localized; JEB-int, junctional EB intermediate; KEB, Kindler EB; RDEB-int, recessive dystrophic EB intermediate; RDEB-inv, recessive dystrophic EB inversed; RDEB-sev, recessive dystrophic EB severe; REBS, recessive EB simplex; SC, subcutaneous. ^aMutation analysis was performed for all 22 patients with EB. Detailed results of the mutation and protein expression analysis are available upon request. ^bSpecified in 21 of 22 cases. ^cAge of two patients stated in Yuen *et al.* ^dSpecified in 15 of 17 cases. ^eType of cSCC not specified in nine invasive cSCCs (12%). ^fTumour diameter not specified in 17 invasive cSCCs (23%). ^gHistological differentiation not specified in 10 invasive cSCCs (13%). ^hDepth of invasion not specified in 17 invasive cSCCs (23%).

The development of large tumours in addition to frequent local recurrences within areas of chronic tissue damage points to a tumour-prone environment facilitating the aggressiveness of EB-cSCCs. The tumours might be discovered only when they are already large because of their indistinct clinical presentation. Therefore, regular skin screenings and biopsies of clinically suspect lesions are imperative for early detection and rapid intervention. In addition, identifying molecular pathways involved in EB-cSCC formation and its aggressiveness, and development of techniques for early *in vivo* tumour recognition, are of utmost importance to provide possibilities for earlier intervention and possibly prevention of this dreadful complication in EB.

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M.C.B. and G.F.H.D. contributed equally to the study.

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