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INVESTIGATIVE REPORT

Mortality and Clinicopathological Features of Cutaneous Squamous Cell Carcinoma in Organ Transplant Recipients: A Study of the Swedish Cohort

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Solid organ transplant recipients have a high incidence of cutaneous squamous cell carcinoma and often develop multiple and aggressive tumours. This retrospective study based on the Swedish organ transplant cohort, focuses on the deaths caused by cutaneous squamous cell carcinoma and aims to elucidate the clinicopathological features of these tumours. The cohort comprised 5931 patients who underwent organ transplantation during the period 1970 to 1997 and were registered in the Swedish In-patient Registry, Cancer Registry and Causes-of-Death Registry. A total of 544 cutaneous squamous cell carcinomas in 201 patients were re-examined. The dominating size of the tumours was 5–10 mm and one-third of the tumours were removed by methods other than excision surgery. Well-differentiated tumours and Clark level IV were predominant. Seven patients died from their tumours, all of which were localized on the head. The principal site of metastasis was the parotid gland. The mean duration between date of transplantation and death was 10.4 years (range 6–17 years). Mortality from cutaneous cell carcinoma was compared with that of the general population. There was a highly increased risk; standardized mortality ratio 52.2; 95% confidence interval 21.0–107.6. However, the mortality rate in the Swedish cohort appears to be lower than what has been reported previously from other countries. *Key words: squamous cell carcinoma; organ transplant recipients; cancer; mortality; epidemiology.*

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It is well known that immunosuppressed organ transplant recipients (OTR) are at increased risk of developing malignant tumours (1–3). For cutaneous squamous cell carcinoma (SCC) a 100-fold increased risk has been shown also in a Nordic population with relatively low level of sun exposure (4). Moreover, cancer in OTR is associated with higher a risk of metastasis than cancer in the general population (5–9). The majority of the cutaneous malignancies are adequately treated locally without significant morbidity. However, a subgroup of the patients develops aggressive SCC with local invasion, early recurrence following treatment, higher rates of metastasis, and increased morbidity and mortality (8, 9). The histopathological features of SCC reported to be more common in OTR include acantholytic changes, early dermal invasion, an infiltrative growth pattern with or without desmoplasia, and Bowen's disease with carcinoma (10). These features as well as the fact that SCC in OTR are also significantly deeper at time of diagnosis (10) might explain their aggressive behaviour.

This retrospective study based on the Swedish OTR cohort (3, 4, 11) focused on the deaths caused by SCC, but also aimed to elucidate the clinicopathological features of the SCCs in the cohort.

PATIENTS AND METHODS

Patients

From the Swedish organ transplant cohort, comprising 5931 patients who underwent transplantation of kidney (5139), liver (397) or other organ (heart, lung and pancreas) (395) during the period 1970 to 1997, as described in detail elsewhere (3, 4), we selected all patients living or dead with cutaneous SCC registered in the national cancer registry. We could identify 273 patients with a total of 656 SCC.

This study was approved by the ethics committee at the Karolinska Institute, Stockholm, Sweden.

Swedish Cancer Registry

The Swedish Cancer Registry, started in 1958, receives reports on all incident malignant tumours diagnosed in Sweden. Reporting by both diagnosing physicians and pathologists is mandatory by law, resulting in registration of more than 98% of all tumours, with histopathological verification of 97% of the tumours (12, 13). For skin tumours these figures are close to 100%. The information available from the registry includes site and histological type of tumour, hospital and pathology department, specimen number and year the specimen was taken. Data from death certificates are also included.

Causes-of-Death Registry

The Causes-of-Death Registry includes information on all deceased persons listed in the parish registers, whether they died in Sweden or abroad. The underlying cause of death is generally determined from data on medical death certificates,

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which were designed in accordance with the internationally established norm.

The individually unique 10-digit national registration number ascribed to every Swedish citizen, ensures accurate identification and follow-up of each patient.

Medical records from dead patients with non-melanoma skin cancer as the principal cause of death were requested and reviewed.

Histopathology examination

Using the histopathological specimen number of all the identified SCC, requests for specimens were sent to all of the 33 pathological laboratories that had reported the cancer. Twenty-six laboratories (79%) sent us the requested specimens along with the original histopathological analysis. By this method 544 SCC were received from 201 patients. These figures represent 83% of the total number of SCC and 74% of the patients with SCC in the Swedish organ transplant cohort. All slides were re-examined by one dermato-pathologist (M-A. H.). In 91 cases the original diagnosis was questioned and a second pathologist (A.T-B.) examined the slides before coming to a consensus. The SCCs were classified as well-differentiated, moderately differentiated or poorly differentiated, depending on the proportion of mature, differentiated cells present in the tumours and the degree of keratinization. In well-differentiated tumours more than 75% of the cells were differentiated, in moderately differentiated tumours 25–75%, and in poorly differentiated tumours fewer than 25%. Classification of depth of the tumours was performed according to Clark levels I–V.

Statistical analysis

The relative risk was estimated by calculating the standardized mortality ratio (SMR). The expected number of deaths caused by SCC was derived from the age, sex and period-specific rates in the Swedish general population (12). We calculated 95% confidence interval (CI) assuming a Poisson distribution (14).

RESULTS

A total of 544 SCC in 201 patients (146 males and 55 females) were re-examined and are characterized in Table I. The dominating size of the removed tumours was 5–9 mm (38.8%) and almost as common was 10–19 mm (34.4%). One-third of the tumours were removed by methods other than excision surgery.

Well-differentiated SCC (53.9%) and Clark level IV (36.8%) were the most frequent categories. Seventy-eight cases (38%) of the well-differentiated SCCs showed kerato-acantomatous features and 22 (7.5%) were of strict follicular origin. Acantolytic variants made up 18 cases (4.3%). A total of 104 (19%) SCC appeared to be derived from actinic keratoses, 9 showed human papilloma virus influences and one was desmoplastic. A total of 3 Merkel cell carcinomas were also found.

Seven patients (6 males and one female) died from their SCC and are characterized in Table II. All were kidney transplant recipients. All tumours were located on the head and 4 of the patients had only one SCC. The principal site of metastasis was the parotid gland.

Table I. *Squamous cell carcinoma (SCC) in organ transplant recipients: tumour size, method of removal, grade of differentiation and Clark level (n=544)*

Tumour characteristics	n (%)
Size (mm)	
< 5	43 (7.9)
5–9	211 (38.8)
10–19	187 (34.4)
20–29	33 (6.1)
≥ 30	8 (1.5)
Information lacking	62 (11.3)
Method of removal	
Excision	375 (68.9)
Punch biopsy	111 (20.4)
Shave biopsy	38 (7.0)
Curettage	20 (3.7)
Grade of differentiation	
Mb Bowen in situ	83 (15.2)
Bowen carcinoma	32 (5.9)
SCC well	293 (53.9)
SCC moderately	121 (22.2)
SCC poorly	15 (2.8)
Clark level	
I	83 (15.2)
II	45 (8.3)
III	98 (18.0)
IV	200 (36.8)
V	43 (7.9)
Information lacking	75 (13.8)

All tumours were poorly differentiated except for one intermediate and one not known. The mean duration between date of transplantation to death was 10.4 years (range 6–17 years) and transplantation to lethal SCC was 8.7 years (range 4–15 years). Duration from lethal SCC to metastasis was 12.0 months (range 5–20 months) and from metastasis to death 8.7 months (range 3–12 months). The mean age at death was 60.7 years (range 49–68 years).

Mortality from SCC was compared with the general population. There was a highly increased risk: SMR 52.2; 95% CI 21.0–107.6.

DISCUSSION

We have reviewed the Swedish OTR cohort ($n = 5931$) with regard to deaths caused by cutaneous SCC and found 7 cases. In comparison with the deaths caused by SCC in the normal Swedish population this figure is highly increased (SMR 52.2). We have also tried to compare the risk of death caused by SCC of a patient with SCC in the Swedish OTR cohort, with a patient with SCC in the normal Swedish population. This risk can only be roughly estimated by using data from the Swedish Cancer Registry. In 2002, it was reported that 17,115 patients with SCC were alive and these were diagnosed in the period 1958 to 2000. Furthermore, in 2001 the rate of deaths caused by non-melanoma skin cancer was 50/100,000. If one assumes that patients

Table II. *Deaths caused by squamous cell carcinoma (SCC) in organ transplant recipients*

Patient/ Sex	Organ/underlying disease	Age at transplant/ death (years)	Total no. of SCC	Site/size (mm) of SCC causing death	Differentiation/local spread	Duration from diagnosis to metastasis/death (months)	Immunosuppression
1/M	Kidney/ glomerulonephritis	36/49	1	Temple/ 20×20	Poorly/ parotid gland and lymph nodes	6/16	Azathioprine Prednisolone
2/M	Kidney ×2/ glomerulonephritis	47 and 52/58	19	Scalp/ 75×40	Poorly/ ear duct	13/16	Cyclosporine Azathioprine Prednisolone
3/M	Kidney/ SLE	51/68	2	Ear/ 6×6	Intermediate/ parotid gland	20/28	Azathioprine Prednisolone
4/M	Kidney/ glomerulonephritis	52/61	2	Ear/ 20×20	Poorly/ parotid gland	16/23	Azathioprine Prednisolone
5/F	Kidney/ nephrosclerosis	53/61	1	Cheek/ 44×35	Poorly/ parotid gland and orbit	5/17	Cyclosporine Azathioprine Prednisolone
6/M	Kidney ×2/ polycystic kidney	54 and 60/62	1	Primary not known	Not known/ submandibular gland	Not known	Cyclosporine Azathioprine Prednisolone
7/M	Kidney/ RA	60/66	1	Ear/ 30×25	Poorly/ parotid gland and lung	12/24	Cyclosporine Azathioprine Prednisolone

SLE: systemic lupus erythematosus; RA: rheumatoid arthritis.

with lethal SCC also prior to death had been diagnosed with SCC the annual rate of deaths in SCC = 8.5 (50×17,115/100,000). The 273 patients with SCC in the Swedish OTR cohort only contribute 916 person years at risk from SCC diagnosis to the end of follow-up. Thus, the expected number of deaths in the OTR cohort (916×8.5/100,000 = 0.078) is to be compared with the 7 deaths observed. This method gives SMR 90 (7/0.078), indicating that the risk of death caused by SCC in OTR affected with SCC is much higher than for normal patients with SCC.

All lethal SCCs were located on the head, and the parotid gland was the principal site of metastasis. This is in line with a recent study of the Irish OTR cohort (9). However, in contrast to that study, four of our patients had only one SCC. In the Irish cohort (n =1553) the six patients who died from their aggressive SCCs had 6–26 tumours (9). The Irish study indicates that patients with multiple SCCs should be followed more closely, in contrast to patients with a single SCC that eventually becomes lethal. It is possible that the follow-up could not prevent lethal SCCs in the patients with multiple SCCs in the Irish cohort. In the Swedish cohort we found a smaller number of cases with lethal SCCs in the patients with multiple SCCs, pointing out possible differences between the two cohorts. Such differences could be (*i*) lower sun exposure in the Swedish cohort (*ii*) fewer individuals with skin type I and II, or (*iii*) differences in immunosuppression regimens. Our study has not controlled for either of these risk factors. In an Australian study of 455 heart transplant recipients, 11 patients died of skin cancer, accounting for 27% of the deaths occurring after the fourth year post-transplant (8). Six died of SCC, 4 of melanoma and one patient of Merkel cell carcinoma. Of the six patients with SCC, invasion of the parotid gland developed in 4 patients and invasion of the external ear developed in 2 patients. This result is in line with our study and again indicates the head as the principal site of lethal SCC and the parotid gland as the principal site of metastasis. However, the magnitude of the deaths caused by SCC in the Australian cohort, 6 lethal SCCs in 455 OTRs (8) and in the Irish cohort, 6 lethal SCCs in 1553 OTRs (9) differs from what was found in the Swedish cohort, 7 lethal SCCs in 5931 OTRs (including 236 heart transplant recipients). Further studies examining differences between these cohorts may provide explanation for the different mortality rates. The occurrence of lethal SCCs on the head and neck supports the role of sun exposure in causation (15). Higher levels of UV-exposure in Australia may have contributed to the increased number of lethal SCCs in this cohort.

The size of the lethal SCCs in our study ranged from 6 to 75 mm in diameter and this is in line with the findings in the Irish cohort (9). Most lethal SCCs in our study were 2 cm in diameter or greater, but tumour size may be misleading and some small tumours behave aggressively (Table II). Nearly half of the number of the removed tumours in our study were small (< 10 mm), but in spite of this, Clark level IV was most common (36.8%) again pointing out the aggressiveness of these tumours in OTR. The previously reported finding (10)

that acantholytic SCCs are common in OTR could not be confirmed in our cohort. We found 4.3% compared with the expected number of 2–4% (16). In the Swedish cohort a large number of small SCCs were removed, not only by excision surgery, but also by punch and shave biopsies and curettage, possibly reducing the risk of aggressive SCC. No such figures are available for the Irish (9) and Australian (8) cohorts. Subsequently, in our study, poorly differentiated SCCs made up only 2.8% of the total number of SCCs, which partly might explain the lower mortality rate in the Swedish cohort of OTR.

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