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Causes of Death in Cutaneous T-Cell Lymphoma Patients

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Keywords
Cutaneous T-cell lymphoma · Mycosis fungoides · Death · Fatal issue · Immunosuppression · Infection · Blastic transformation · Comorbidities

Abstract
Background: The advancing evolution toward a Th2 immune environment confers a progressive immunosuppression in patients with longstanding cutaneous T-cell lymphoma (CTCL). The conjunction of the disease-related immunosuppression as well as the immunosuppressive character of some CTCL treatments increase the risk of infectious and neoplastic diseases, sometimes with fatal outcomes. ***Objectives:*** The aim of the study was to prospectively study the causes of death in a cohort of CTCL patients, in a tertiary university skin cancer center. ***Methods:*** All CTCL patients who died between 2008 and 2020 were included. The cause of the death was classified as directly or indirectly related or unrelated to CTCL. ***Results:*** Over the study period, 31 (13F/18M) patients with CTCL died (mean age: 75.2 years), mean delay between diagnosis and death: 3.2 years (min: 1, max: 12 years), 58.1% of death causes were classified as indirect (infection), 12.9% directly related (blastic transformation), 22.5% unrelated, and 6.5% of unknown cause. 51.6% of mycosis fungoides (MF) patients who died had early-stage disease (1A–2A) or were on remission. 45.2% of dead patients had advanced-stage MF (2B–4B). Mean CRP level is increased in patients who died from infection whereas LDH level increased in patients with blastosis. A tertiary center is expected to manage of a higher proportion of CTCL patients with advanced-stage disease. ***Conclusions:*** As infection represented more than 50% of the causes of death in CTCL patients, particular attention should be given to preventive measures such as anti-infective vaccination. Regular surveillance of CRP and LDH levels could be helpful for follow-up of MF patients, respectively, with regards to infection and blastosis.

Introduction

Among the primary cutaneous T-cell lymphomas (CTCL), mycosis fungoides (MF) is the most frequently observed type, representing about 60–70% of the cases [1, 2]. The incidence rates for MF are 5.6 per million persons for males and 3.6 for females, indicating that MF typically affects men 2 times more often than women [3]. MF generally occurs in the elderly population [4].

Although the overall prognosis of early-stage MF is good to excellent, advanced-MF presents a high disease burden and mortality rate [5]. In fact, T1 (less than 10% of body surface area [BSA] involvement), T2 (more than 10% of BSA involvement), T3 (tumor stage), and T4 (erythroderma) stage MF have 10 years survival rates of 100%, 67–96%, 51–80%, and 20–41%, respectively [1, 4].

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Early-stage MF is usually behaving as an indolent skin disease, with flares and remission periods, but nonetheless represents a significant and long-term impact on the quality of life of the patients. Treatments in this stage are commonly based on skin-directed therapies. The cutaneous CTCL lesions are prone to secondary infections [5, 6]. Furthermore, topical corticosteroids, UVB and PUVA, as well as topical chemotherapies can additionally increase local immunosuppression [7, 8].

Advanced-stage MF is associated with a progressively declining systemic immunocompetence [7–9]. Furthermore, some of the systemic medications used for MF, such as methotrexate, interferon, mogamulizumab, and brentuximab vedotin, also exhibit immunosuppressive properties, increasing infection, and neoplasia risks [7, 8].

Hence, death causes of patients with MF may result in systemic infection, especially with *Staphylococcus aureus* or *Pseudomonas aeruginosa* infections [5]. These patients are also at increased risk for secondary neoplasia, such as higher-grade non-Hodgkin lymphoma, Hodgkin disease, colon cancer, as well as cardiovascular and pulmonary complications. Blastic transformation of MF not only seems rare but also may constitute a cause of death [10, 11]. We were interested to assess the causes of death in a prospective study of patients with MF in a tertiary skin cancer university setting.

Materials and Methods

Patients

All the patients with CTCL were prospectively followed between January 1, 2008 to December 31, 2020. All disease stages were included. Patients who died in this study period were included and the following data were recorded: age at death, gender, delay between the first diagnostic confirmation by a clinical, histological, immunohistochemical (IHC) and monoclonal T-cell receptor rearrangement, eventual associated risk factors, the stage at the first diagnosis, the stage at the death, an eventual variation of the T classification, the treatment of the CTCL, and the cause of the death and an eventual link. The death links were classified as scores: (1) considered unrelated to the CTCL and the CTCL related treatments, (2) considered indirectly related to the CTCL disease and or treatment (infection, sepsis, solid cancers other than CTCL), or (3) directly related to the CTCL (blastic transformation or CTCL disease progression). Disease evolution was classified according to the T-stage variation at diagnosis and death: progressing disease: $T_{Diagnosis}<T_{Death}$, a stable disease: $T_{Diagnosis} = T_{Death}$, or a regressing disease: $T_{Diagnosis}>T_{Death}$. As surrogate markers of immunosuppression before death, the CRP (normal: <5.0 mg/L) and LDH (normal: 125-220UI/L) levels were searched for in the last available blood samples before death.

Results

A total of 120 patients with CTCL were followed. Over the study period 31 (26%) (13F/18M) patients with CTCL died (mean age: 75.2 years, min: 54 years, max: 94 years), including 29 patients with classical MF, 1 cutaneous LNH CD30+, and 1 nasal type CTCL. The major findings of the individual patients are presented in Table 1.

The mean delay between the final histological, IHC, and T-cell receptor diagnosis and death was 3.2 years (min: 1 year, max: 12 years). The T staging of the deceased patients at diagnosis were the following: T1 (<10% body surface area [BSA]): 3.2% (1/31), T2 (>10% BSA): 58% (18/31), T3 (tumor stage): 19.4% (6/31), and T4 (erythrodermic stage): 19.4% (6/31). The respective figures at death are 12.9% (4/31), 32.2% (10/31), 19.4% (6/31), and 22.6% (7/31).

The disease evolution according to the T stage was the following: a progressing disease ($T_{Diagnosis}<T_{Death}$): 22.6% (7/31), a stable disease ($T_{Diagnosis} = T_{Death}$): 41.9% (13/31), or a regressing disease ($T_{Diagnosis}>T_{Death}$): 32.3% (10/31). Of the deceased patients, 51.6% (16/31) presented an underlying immunosuppression or prior or concomitant neoplastic comorbidities. The neoplastic diseases included 4 breast cancers, 3 mucosal squamous cell cancers, 3 chronic lymphocytic leukemias, one renal carcinoma, one melanoma, and one meningioma.

The cause of death of 22.6% of the patients (7/31) was judged not related to CTCL (score 1). A total of 58.1% patients (18/31) died from a pulmonary infection or sepsis (score 2) and 12.9% of the patients (4/31) died directly from a local and/or systemic progression of their CTCL disease (blastic transformation [Fig. 1a–c] or metastasis) (score 3). Two patients died of unknown cause (6.5%).

In the first group (death unrelated to the CTCL), there were 71.4% (5/7) of the patients with a regressing disease and 28.6% (2/7) patients with a stable disease. In the second group considered indirectly related to the MF 38.9% (7/18) of the patients had a progressive disease, 27.8% (5/18) had a regressing disease, and 33.3% (6/18) had a stable disease. For the patients who died directly from their CTCL, there were 75% of the patients who had a progressive disease and 25% who presented a stable disease. The disease progression status seems to be correlated with the cause of death. These results are summarized in Table 2.

Among the 31 deceased patients, 16/31 (51.6%) had an early-stage MF (1A–2A) or a disease in remission (T0N0M0B0) at the time of the death. 14/31 (45.2%) had advanced-MF (2B–4B). None of the early-stage patients

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Table 1. Summary of the demographical, clinical, pathological data, and death causes of the individual patients

Patients	Age at death/ gender	Delay diagnosis => death	Risk factors	Stage at histological diagnosis	Stage at death	T variation	CTCL treatment at death	Cause of death	Score
1	91/F	1 year		T3N0M0B0 2b	T0N0M0B0	↘	MTx, surgery, intralesional CCS	Bacterial bronchopneumonia and cardiac decompensation	2
2	56/F	1 year	Breast cancer	T2N0M0B0 1b	T4N0M0B0 3a	↗	MTX	Sepsis (entry portal: ENT area)	2
3	72/F	1 year	Breast cancer	T2N0M0B1 1b	T3N0M1B1 4b	↗	MTX	Bacterial pneumonia with sepsis and lepto-meningeal infiltration	2
4	69/M	8 years	Clear cell renal carcinoma	T3N0M0B0 2b	T2N0M0B0 1b	↘	MTX	Renal cancer metastasis: lungs, liver, and skin	1
5	82/F	4 years		T2N0M0B0 1b	T4N2M0B0 $4a_1$	↗	TBEBT	Bacterial pneumonia and blastic transformation of MF	2, 3
6	69/M	5 years	SCC fibromyoblastic transformation	T2N0M0B0 1b	T1N0M0B0 1a	↘	MTX	Bacterial pneumonia	2
7	73/M	2 years	Laryngeal neoplasm	T1N0M0B0 1a	T4N1M0B2 $4a_1$	↗	CHOP	Complication during CHOP chemotherapy	3
8	89/M	2 years	CLL	T2N0M0B0 1b	T3N0M0B0 2b	↗	MTX	Blastic transformation	3
9	81/M	1 year		T2N0M0B0 1b	T1N0M0B0 1a	↘	Acitretin	Cranial traumatism with extradural hematoma	1
10	66/M	4 years	SCC head and neck	T4N1M0B0 3b	T4N1M0B0 3b	⇔	Acitretin, TBEBT	Sepsis following pulmonary and skin infection	2
11	54/F	4 years	Meningioma	T3N1M0B2 2b	T3N3M1B2 $4a_2$	⇔	Brentuximab	Pleural infiltration and carcinomatous lymphangitis	3
12	77/F	4 years		T4N0M0B0 3a	T1N0M0B0 1a	↘	Inf + MTX	Cardiac failure with auricular fibrillation	1
13	84/F	2 years		T2N0M0B0 1b	T2N0M0B0 1b	⇔	MTX	Stroke	1
14	68/F	1 year		T4N1M0B0 3a	T4N1M0B0 3a	⇔	Acitretin	Sepsis following pulmonary and skin infection	2
15	94/M	ND	IgM gammapathy	T2N0M0B0 1b	T2N0M0B0 1b	⇔	MTX	Cardiac failure	1
16	82/M	1 year	CLL	T2N0M0B0 1b	T3N0M0B0 2b	↗	MTX	Pulmonary infection with cardiac failure	2
17	72/M	4 years	Psoriasis + Ciclosporin	T3N0M0B0 2b	T3NxM1B0 4b	⇔	MTX	Sepsis following pulmonary infection and cardiopulmonary failure	2
18	94/F	6 years	Breast cancer	T2N0M0B0 1b	T1N0M0B0 1a	↘	Bexarotene	Infectious exacerbation of chronic obstructive bronchopneumonia	2

Table 1 (continued)

Patients	Age at death/ gender	Delay diagnosis => death	Risk factors	Stage at histological diagnosis	Stage at death	T variation	CTCL treatment at death	Cause of death	Score
19	75/F	2 years	Breast cancer	T2N0M0B0 1b	T2N1M0B0 2a	⇔	Bexarotene	Septic choc with *Staph aureus* bacteremia	2
20	81/M	8 years	CLL	T2N0M0B0 1b	T0N0M0B0	↘	MTX	Deterioration of general condition following femur fracture	1
21	55/M	3 years	Cardiomyopathy	T4N0M0B0 3a	T2N0M0B0 1b	↘	Bexaroten	Septic choc with *Staph aureus*	2
22	79/F	1 year		T2NxM0B0 1b	T2NxM0B0 1b	⇔	PUVA	Septic choc after mitral *MSSA* endocarditis and pulmonary infection	2
23	84/M	12 years		T2N0M0B0 1b	T0N0M0B0	↘	Remission	Severe aortic stenosis and euthanasia	1
24	89/M	1 year	Melanoma	T2,3N0M0B0 2b	?		Acitretin	?	?
25	81/M	4 years		T2N0M0B0 1b	T2N0M0B0 1b	⇔	MTX	Pulmonary infection followed by bacterial sepsis	2
26	71/M	4 years		T2N0M0B0 1b	T2N0M0B0 1b	⇔	Acitretin + PUVA	COVID-19	?
27	52/F	5 years		T2N0M0B1 1b	T3,4N1M0B1 3b	↗	Chemotherapy GEMZAR	Septic choc with *Staph aureus* bacteremia	2
28	67/M	1 year		T4N0M0B0 3a	T4N0M0B0 4a	⇔	MTX, topical steroids	?	?
29	65/M	2 years		T2N0M0B0 1b	T2N0M0B0 1b	⇔	Miniallograft, PUVA	Sepsis followed by multisystemic failure	2
30	74/M	4 years		T4N0M0B0 3a	T2N0M0B0 1b	↘	Brentuximab	Bronchopneumonia with SARS-COV2 and *Pseudomonas aeruginosa*	2
31	84/F	1 year		T3N0M0	T3N0B0	⇔	Surgery, radiotherapy	Sepsis, entry portal: eroded nose lesion	2

F, female; M, male; MF, mycosis fungoides; MTX, methotrexate; CCS, corticosteroids; ENT, ear, nose, throat; TBEBT, total body electron beam therapy; SCC, squamous cell carcinoma; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; CLL, chronic lymphocytic leukemia; Inf, interferon; PUVA, psoralen ultraviolet A; GEMZAR, gemcitabine; SARS-COV-2, covid 19; NK, natural killer.

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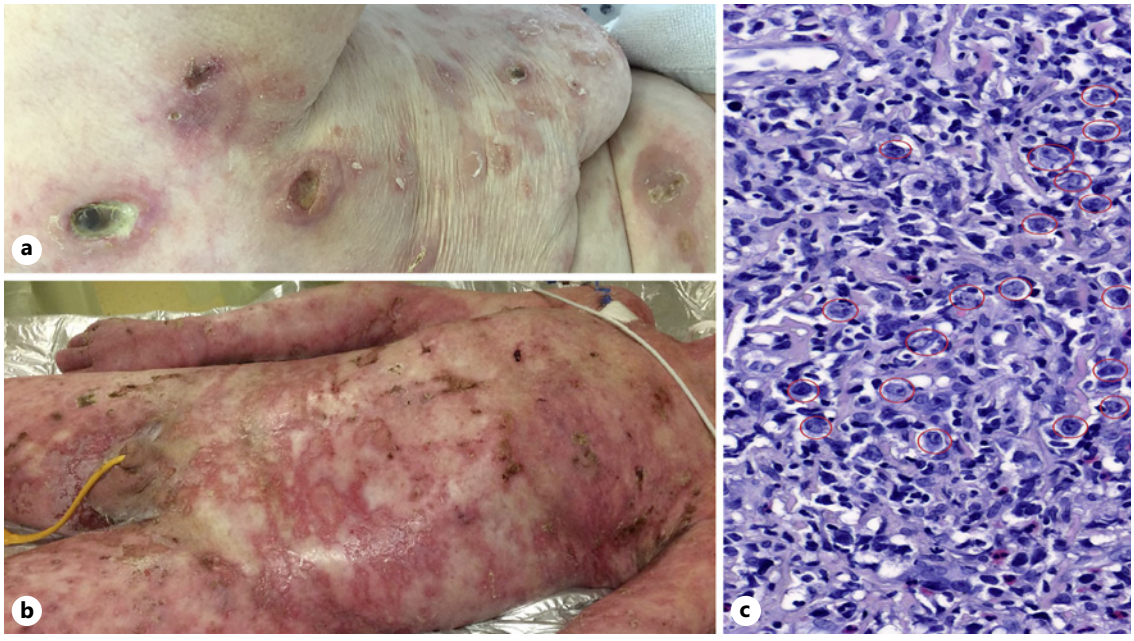

Fig. 1. a Blastic transformation with lethal issue in an elderly female patient (patient 5). **b** Blastic transformation of widespread CTCL (patient 8). **c** Histology illustrating the large cell transformation, see red circles (patient 5, H/E, × 40).

Table 2. Score classification of patients by cause of death

Score 1 (not related to CTCL)		Score 2 (infection)			Score 3 (blastic transformation or CTCL progression)		Unknown cause	
7 patients (22.6%)		18 patients (58.1%)			4 patients (12.9%)		2 patients (2.5%)	
5/7 (71.4) ↘	2/7 (28.6) ⇔	7/18 (38.9) ↗	6/18 (33.3) ⇔	5/18 (27.8) ↘	3/4 (75) ↗	1/4 (25) ⇔	1/2 (50) ⇔	1/2 (50) ?
Majority of patients with a regressing disease		Majority of patients with a progressive or stable disease			Majority of patients with a progressive disease			

died from blastic transformation. The main cause of death in these patients was infection (10/16 patients, 62.5%).

CRP and LDH levels were retrieved from the last available blood samples before death as surrogate markers of immunosuppression. From the 18 patients with an available blood sample, 3 patients had a score of 1 (mean CRP = 18.9 mg/dL, mean LDH = 239UI/L), 14 patients had a score of 2 (mean CRP = 162.3 mg/dL, mean LDH = 561.7UI/L), and 1 patient had a score of 3 (CRP = 30 mg/dL, LDH = 1165UI/L). In general, patients who died from infection seemed to present an increased CRP level, whereas patients who died from blastosis presented an increased LDH level. Table 3 resumes the characteristics of the 18 patients: CRP and LDH levels, cause of death and score.

Discussion

Many studies have been focused on secondary neoplasms in CTCL patients but information about precise death causes in patients with MF and Sézary syndrome is

Table 3. Summary of the characteristics of the 18 patients with available blood samples: CRP and LDH levels, cause of death, and score

Patients	CRP (0–5 mg/L)	LDH (125-220UI/L)	Cause of death	Score
1	15.8	185	Bacterial bronchopneumonia and cardiac decompensation	2
2	222.3	435	Sepsis (entry portal: ENT area)	2
3	28.3	845	Bacterial pneumonia with sepsis and lepto-meningeal infiltration	2
4	201.8	190	Bacterial pneumonia	2
5	6.7	277	Cranial traumatism with extradural hematoma	1
6	194.8	358	Sepsis following pulmonary and skin infection	2
7	30	1,165	Pleural infiltration and carcinomatous lymphangitis	3
8	1.6	256	Cardiac failure with auricular fibrillation	1
9	75.6	/	Pulmonary infection with cardiac failure	2
10	390.8	1,199	Sepsis following pulmonary infection and cardiopulmonary failure	2
11	173.1	/	Infectious exacerbation of chronic obstructive bronchopneumonia	2
12	350.4	1,063	Septic choc with *Staph aureus* bacteremia	2
13	48.5	186	Deterioration of general condition following femur fracture	1
14	247.4	/	Septic choc after mitral *MSSA* endocarditis and pulmonary infection	2
15	33.9	/	Pulmonary infection followed by bacterial sepsis	2
16	227.3	194	Septic choc with *Staph aureus* bacteremia	2
17	83.5	586	Sepsis followed by multisystemic failure	2
18	55.9	/	Bronchopneumonia with SARS-COV-2 and *Pseudomonas aeruginosa*	2

limited [12]. Bacterial skin infections are a common cause of morbidity in patients with CTCL [6]. Septicemia and bacterial pneumonia seem to represent the major infectious causes of death and are usually nosocomial. Indeed, infections are usually involved in more than 50% of death in CTCL patients [5, 13] which is similar to our study cohort where around 6 out of 10 patients died of an infectious cause. An advanced disease stage of the CTCL was considered as the most important risk factor for cutaneous and systemic infections [5, 13]. Our study however demonstrated that not only advanced-stage CTCL patients are at risk for death from an infectious cause.

In our cohort, 72.2% of the patients who died from an infection had a progressive or stable disease. Another important fact is that the use of immunosuppressive agents in MF patients furthermore contributes to the risk of the infection [14, 15], especially in patients with advanced disease already immunocompromised by the disease-related Th2 cytokine profile [6].

In a cohort of 489 CTCL patients, between 15% and 20% died of CTCL or related complications [15]. In this study, the relative survival of CTCL patients deteriorates with increasing disease stage, although T3 and T4 stages presented highly similar survival rates. They concluded that the great majority of patients with CTCL do not die of their disease [15]. Another study demonstrated that the risk for disease progression to a more advanced-stage or death due to MF is linked to T stage, just like the risk of extracutaneous disease [9]. In our cohort, 75% of the patients who died from blastic transformation or extracutaneous MF had a progressive disease. Studies have demonstrated that an advanced-stage at the moment of the transformation is the predominant risk factor of poor outcome, with a 5-year survival rate of 26.9% in stage 2B and 10.6% in stage 4. The documentation of histological and immunohistochemical features of progressive MF is important to identify early blastic transformation [11].

The increased risk of lymphoma in patients with MF or SS is known [16]. In a cohort of 1,798 MF patients followed from 1973 to 2001, there were 197 s malignancies. Significantly increased risk was seen for Hodgkin disease (standardized incidence ratio [SIR] = 17.14) and non-Hodgkin lymphoma (SIR = 5.08). Elevated risk was observed for melanoma (SIR = 2.60) and urinary cancer (SIR = 1.74) [17]. A retrospective study of 2 population-based cancer registries for patients with MF/SS diagnosed before 30 years evaluated the incidence and outcomes of these patients. There was an increased risk of all types of second cancers (SIR = 3.40), particularly lymphoma (SIR = 12.86) and melanoma (SIR = 9.31). Even if patients with MF before 30 years have a favorable outcome, there is a significant excess risk of second primary cancers. Long-term follow-up is therefore essential [17].

A Finnish study including 144 patients with CTCL showed that the 3 most common causes of death were the CTCL itself, coronary artery disease, and lung cancer. Among the total cohort 21,5% (31/144) of the patients

died, 12 from their cutaneous lymphoma, 5 from coronary diseases, 4 from lung cancer, 3 from colon or prostate cancer, 1 from myocardial infarction, 2 from cerebral strokes, 2 with alcoholic hepatitis, and 1 with intoxication [12]. Hence, in this cohort, 8/31 patients (25.8%) died from cardio-vascular comorbidities which is higher than in our study where 4/31 patients (12.9%) died from cardiovascular issues (2 cardiac failures, 1 stroke, 1 severe aortic stenosis). It was suggested that the chronic systemic inflammation seen in the MF patients represented an important contributor to metabolic diseases as hypertension, type 2 diabetes mellitus, and atherogenesis. Further studies in larger populations would be necessary to evaluate the part of cardiovascular comorbidities in death of MF patients [12]. In addition, this study mentioned a high proportion of patients dying from their CTCL itself whereas in our cohort only 12.9% (4/31) patients directly died from CTCL.

A total of 74.2% (23/31) of the patients had a lower T score or stable disease at death. The proportion of early-MF and advanced-MF at the time of the death is relatively similar in our study. It means that the disease stage might not always be predictive of a bad prognosis or death. Infection remains the leading cause of death in early-stage patients. Anti-infective care should therefore be included early in the disease management.

Another study reporting on 28 patients followed over 12 years mentioned 13 lethal issues, particularly in advanced disease stages. Among these patients, 2 who died were atypical as they rapidly progressed from stage 1A disease [18].

One limitation of the study is that our study cohort included probably more severe disease stage patients linked to the tertiary care center setting as illustrated by the relatively short mean delay of 3.2 years between diagnosis and death whereas the overall prognosis of MF is good.

In conclusion, death in CTCL patients not only occurs in patients with advanced disease stages but also in patients with stable disease or even improved disease. Hence, a particular attention should be given to both early and advanced-stage CTCL patients to infectious disease preventive measures, including vaccination. Regular surveillance of CRP and LDH levels could be helpful for follow-up of MF patients, respectively, with regards to infection and blastosis.

Statement of Ethics

The study was performed in accordance with the Helsinki convention on human rights. The patients were informed about the procedures and were invited to fill in a medical questionnaire. All the patients signed the informed consent forms. Ethical approval was not required, due to the local directives of the University Hospital-Faculty Ethics Committee of Liège, given the observational and non-interventional nature of the study (Ethics Committee of the CHU, Sart Tilman (707), Avenue de l'Hôpital, Liège, B-4000, Belgium). Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

E.L., P.C., J.S., and A.F.N. have nothing to disclose.

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Author Contributions

E.L., P.C., J.S., and A.F.N. all participated equally in the concept and design, as well as in the final drafting of the manuscript. Eve Lebas and Arjen F. Nikkels both provided significant contributions to the conception and design, the analysis and interpretation of the data, and to the drafting the final article and revising it critically for important intellectual content, and on the final approval of the version to be published. Patrick Collins and Joan Somja critically revised the intellectual content and approved the final version to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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