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Malignant peripheral nerve sheath tumours in NF1: Improved survival in women and in recent years

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ABSTRACT

Background: Malignant peripheral nerve sheath tumours (MPNST) are the main soft tissue malignancy associated with neurofibromatosis 1. These uncommon tumours are known to occur at high frequency and lead to poor survival. Our aim was to determine risk of MPNST in NF1 patients, and survival rates.

Methods: The incidence of MPNST in NF1 was identified through the NF1 genetic register and The North West Cancer Intelligence Service (NWCIS). Data were used to generate incidence and survival curves. Strict regional boundaries were adhered to avoid ascertainment bias. Kaplan–Meier curves were used to determine five and ten-year survival.

Results: Of the 1059 NF1 patients 52 developed MPNST (30 cases in females and 22 in males), 43 cases were resident within the strict regional boundary. The risk of MPNST was 10.2% in males and 12.7% in females by age 70 years ($p = 0.9$), with a statistically better survival in females than males (5 and 10 year survival 46% and 41.5% versus 22% and 8.2%; $p = 0.05$). Survival was also significantly improved for patients diagnosed in the last 14 years compared to the previous 13-year period ($p = 0.03$).

Conclusion: With fifteen strict regional MPNSTs in the fourteen years since our previous population study an annual incidence of above 1 per 1000 NF1 patients has now been maintained over a 27-year period. No significant increase in risk of MPNST in females compared to males was found, though the difference in survival is intriguing. Male survival is particularly poor with <10% alive at 10 years.

1. Introduction

The autosomal dominant disorder neurofibromatosis 1(NF1) has a generally shortened life expectancy among its patients. The main soft tissue malignancy associated with NF1 is malignant peripheral nerve sheath tumour (MPNST); these are uncommon tumours that substantially vary in clinicopathologic presentation.[1] In particular, the cutaneous form of MPNST is very rare[5–7] and is often a secondary form of larger underlying tumours. These are often aneuploidy and poorly defined, with only half exhibiting schwannian differentiation by immunohistochemical methods. Conversely,

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Triton tumours (tumours exhibiting mesenchymal primarily rhabdomyosarcomatous differentiation) are more commonly associated with neurofibromatosis 1.[8] Past studies have shown that 20–50% of patients with MPNST also have NF1,[2–4] with a lifetime risk between 8% and 13% of MPNST in NF1.[4] However, there has been limited evidence of association with other tumour prone disorders, with only case reports of associations with *TP53* mutations[9] and schwannomatosis.[10]

To date there have been few studies that have estimated the differences between NF1 males and females, nor any that have determined temporal trends in NF1 related MPNST survival. We, therefore, interrogated our NF1 genetic resister and the North West Cancer Intelligence Service (NWCIS) to assess NF1 MPNST incidence over a 27 year period and assess trends in survival.

Table 1 – Diagnostic criteria for NF1 (two or more must be present).

1.	Six or more café au lait macules, the greatest diameter of which is more than 5 mm in prepubertal patients and more than 15 mm in postpubertal patients
2.	Two or more neurofibromas of any type, or one plexiform neurofibroma
3.	Axillary or inguinal freckling
4.	Optic glioma
5.	Two or more Lisch nodules
6.	A distinctive osseous lesion such as sphenoid dysplasia or pseudarthrosis
7.	A first-degree relative with NF1 according to the preceding criteria

2. Patients and methods

Established in 1989 the North West Regional Genetic Register Service (GR) offers long term follow up to NF1 patients and their families, including updating patients about new research and research opportunities. At present the registry covers a regional population of 4.1 million in the North West (based around Manchester), and is now part of a nationally commissioned service in England. To corroborate an NF1 diagnosis hospital notes, including histology reports and details of other typical NF1 disease features (Table 1), were reviewed (e.g. café-au-lait macules and neurofibromas with respect to the US National Institutes of Health diagnostic criteria).[11] The North West Cancer Intelligence Service (NWCIS) is an established cancer registry that uses pathology records and death certificates to ascertain malignancies and benign CNS tumours. The NWCIS covers the same region of North West England as the GR and has been used to verify cancers in the NF1 registry; including the previous review for patients with MPNST (ICD-0: M9540/3 and 9560/3) from 1984 to 1996.[4] In addition, we reviewed hospital notes for all patients with MPNST who were identified for the study to confirm diagnosis.

All deceased cases were identified from the registries and their details used to calculate survival rates. Information on cause of death was obtained from death certification. Follow-up was censored on 1st April 2010. Staging of MPNST was performed using the American Joint Committee on Cancer (AJCC)

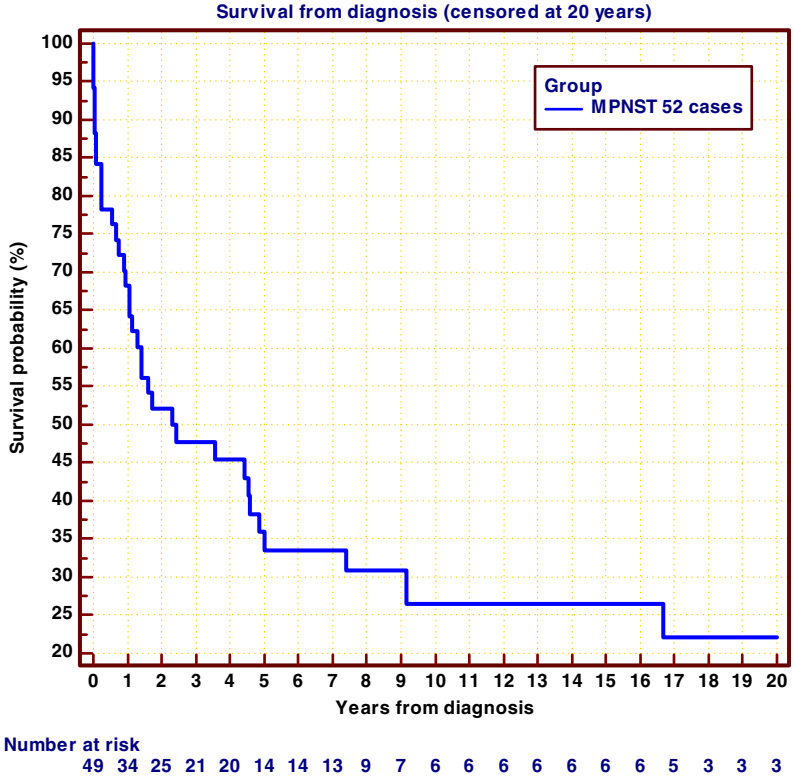

Fig. 1 – Kaplan–Meier analysis of survival for NF1 MPNST patients.

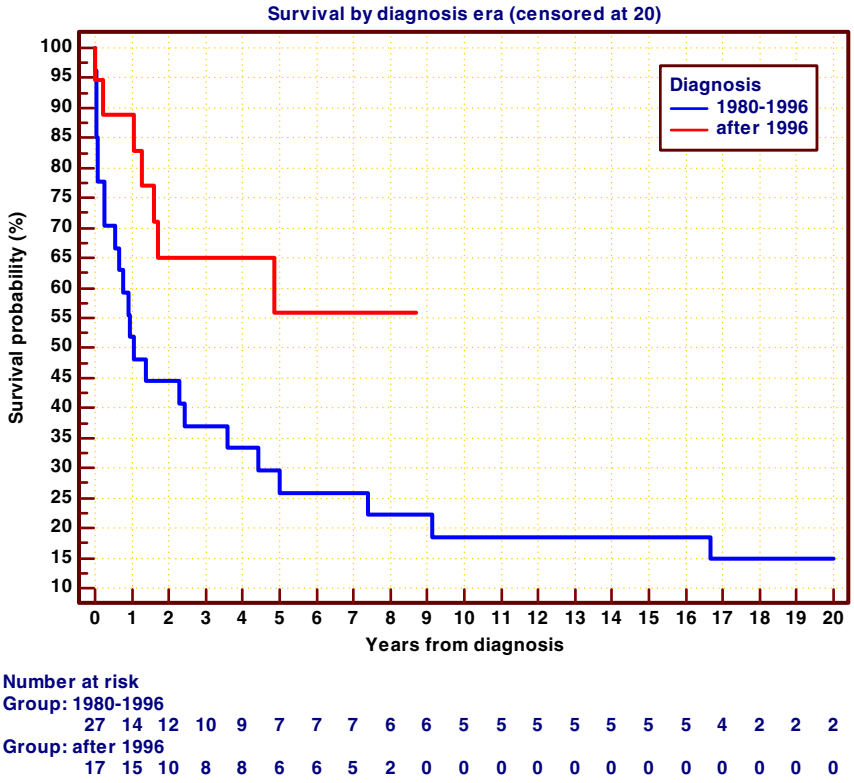

Fig. 2 – Kaplan–Meier analysis of survival for NF1 MPNST patients comparison of those diagnosed from 1980–1996 to 1997–2010. (Wilcoxon [Gehan] statistic, *P* = .05).

staging system for soft tissue sarcoma. To avoid ascertainment bias only those resident in a strict regional boundary were used for such analysis as the MPNST incidence curves. However, NF1 MPNST cases that were identified on the periphery of the region during the study period were included in the survival analysis. Kaplan–Meier curves were used to determine five and ten-year survival. The Mann–Whitney U test and Wilcoxon (Gehan) statistic were used to test between-group differences in age at diagnosis and survival.

3. Results

Of the 1254 NF1 patients known to the genetic resister 52 have developed MPNST; 43 of these cases were resident within the strict regional boundary of a population of 1059 patients. There were 30 cases in females and 22 in males. Amongst the strict regional population 17/473 males and 26/586 females had developed MPNST. Since 1996, 15 strict regional cases of MPNST have been recorded maintaining an incidence rate of above 1 per 1000 NF1 patient per year as 1010 NF1 patients were alive at some point after 1996.

3.1. *Survival*

Fig. 1 shows the survival from the diagnosis of NF1 patients with MPNST. The five and ten-year survival rates were 33.5% and 23.5% for the 52 NF1 MPNST patients (95% confidence interval, 26.5–40.5% and 16.5–30.5%) (median survival, 2.4 years). There was an improved survival for those diagnosed in most recent years (1997–2010) compared to the original cohort of 1980–1996 (Fig. 2: $p = 0.03$). There was also an improved survival for women compared to men with 5 year survivals of: 46% (95% CI 37–55%) compared to 22% (95% CI 12.6–31.4%) (Fig. 3: $p = 0.05$). This survival advantage was due to earlier stage at diagnosis in females and in those diagnosed since 1996 (Table 2). Tumour size was not always identifiable from records so some deeper location tumours had to be estimated between stage 2 and 3. The table includes three recent non-regional females who did not contribute follow up data to the figures. Fifty-six and 54 percent of both those diagnosed between 1980 and 1996 and males presented with AJCC stage 4 with metastatic disease. In contrast this fell to 36% of women and 23% of the more recent cohort (1997–2010).

3.2. *NF1 MPNST lifetime risk*

The cumulative risk of MPNST was 11.7% (95% CI 9.7–13.7%) by age 70 years based upon the strict regional population of 1059 NF1 individuals. However, due to the small number of patients (34) alive beyond 70 years-of-age the robustness of incidence after this point is influenced by a single case in a female aged 77 years. There was no significant difference in incidence for women versus men (Fig. 4). The risk of MPNST was 10.2% (95% CI 7.2–13.2%) in males and 12.7% (95% CI 9.7–15.7%) in females by age 70 years ($p = 0.9$).

4. Discussion

A number of previous studies have investigated the association between MPNST and NF1.[2–4,12–16] However, this study

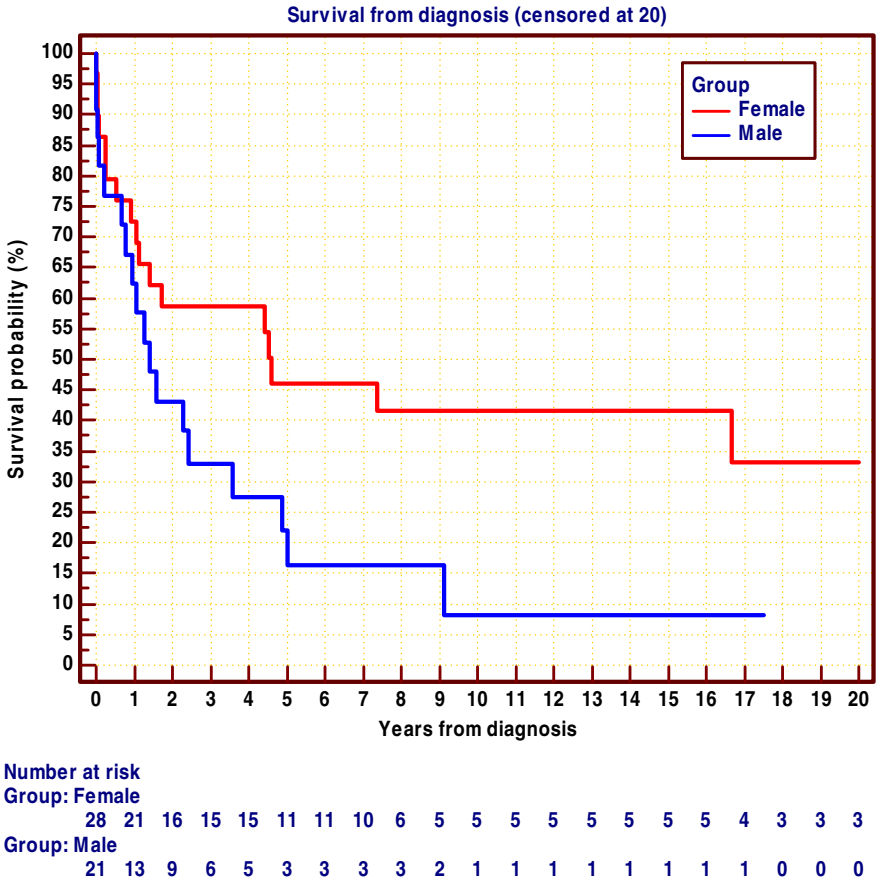

Fig. 3 – Kaplan–Meier analysis of survival for NF1 MPNST patients comparison of males versus females (Wilcoxon [Gehan] statistic, *P* = .03).

Table 2 – Stage and 1-year mortality by group year and gender.

	1980–1996	1997–2010	Male	Female
Number	27	22	22	33
Stage 1	4	7	1 (5%)	11 (33%)
Stage 2	6	9	8 (36%)	8 (24%)
Stage 3	2	1	1 (5%)	2 (6%)
Stage 4 (metastases at presentation)	15 (56%)	5 (23%)	12 (54%)	12 (36%)
Death within 1 year of diagnosis	13 (48%)	3 (13%)	9 (41%)	8 (24%)

Six cases were diagnosed before 1980 when the Registry was not systematically checked.

documents one of the largest population samples of MPNST in NF1, doubling the number of cases in our previous article.[4] With fifteen MPNSTs in our regional population in the fourteen years since our last population based study,[4] we have further strengthened our estimate of lifetime risk. An annual incidence of above 1 per 1000 NF1 patients has now been maintained over a 27-year period. To support the robustness of the calculated estimates strict regional borders were adhered to for all MPNST cases used in the incidence analysis.

Although more cases of MPNST occurred in females there was no significant increase in risk for women compared to men with estimates of between 10% and 13% by 70 years-of-age. The similarity of the risks is partly explained by the smaller number of males in the regional population, especially at older ages.

The difference in survival for men versus women is intriguing. Male survival is particularly poor with <10% alive at 10 years. Survival in MPNST is primarily driven by metastatic spread which is primarily due to size, depth and grade of the presenting tumour. Assuming grade and depth is largely uninfluenced by delay in treatment it could be postulated that earlier presentation with symptoms in women could be a major factor in this difference. This would also be supported by the improved survival in the last 14 year period. Both of these hypotheses are supported by the earlier stage at diagnosis seen in Table 2. No survival advantage was reported for females with MPNST in a recent paper,[17] however, the paper only reported on treatment of late stage disease and was not specific for NF1. Although the report showed a better response rate in males it is of interest that there were

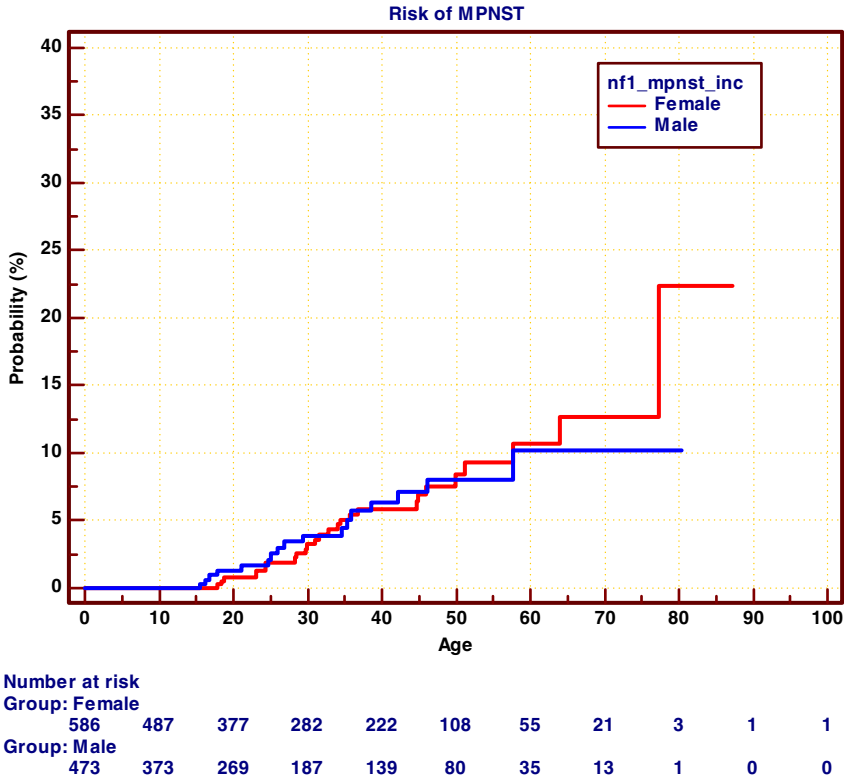

Fig. 4 – Cumulative incidence of MPNST in male and female NF1 patients within the strict North West region boundaries.

statistically significantly more males than females with advanced tumours to enter the study. There have been no major improvements in treatment in MPNST to account for the recent improvement in survival and the likely explanation shown by an earlier stage is earlier presentation. There has, nonetheless been a greater awareness amongst our NF1 patients of the potential risk and the need to present early with symptoms.

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Conflict of interest statement

None declared.

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