Sarcomas in the Dutch LFS population; data from the national screening of TP53 germline mutation carriers at the Netherlands Cancer Institute

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BACKGROUND

Li-Fraumeni syndrome (LFS) is a rare, autosomal dominant cancer predisposition syndrome, associated with germline mutations in the TP53 gene and a variety of histologically different tumours, of which early-onset breast cancer, sarcomas, leukaemia and brain tumours tend to occur most frequently. In this study, we report on sarcoma incidence in the LFS population in the Netherlands, based on data of the Netherlands Cancer Institute (NCI), the national referral centre for LFS.

METHODS

Study cohort

The study cohort consisted of all subjects that are:
- Known in the clinical genetics department in the NCI to have a confirmed pathogenic TP53 germline mutation.
- Participating in the LFS screening program in the NCI between October 2011 and October 2020.

Data extraction

The following data was retrospectively collected from patient files:
- Patient characteristics: Age, sex and family history
- Tumour characteristics: Histology, age at time of diagnosis (AAD) and, in case of sarcoma, histology subtype and tumour site.
- Specific TP53 germline mutation variant.

LFS screening program at the NCI between Oct 2011 and Oct 2020
- Complete physical examination
- Complete blood count and lactate dehydrogenase
- Whole body MRI
- MRI breast
- MRI brain
- Colonoscopy

RESULTS

Patient group
- Between October 2011 and October 2020, a total of 119 carriers, confirmed to carry a TP53 germline mutation, participated in the screening program.
- Of these 119 subjects, 69 were female (58.0%) and 50 were male (42.0%).
- 78 (66.5%) of them had a personal history of cancer, with 29 (24.4%) patients having multiple cancer diagnosis in their medical history. The incidence of tumour types showed a classic LFS distribution, with breast cancer (34.7% of all cancers), sarcomas (24.0%) and brain tumours (6.6%) being the most frequently diagnosed.

Tumour characteristics: Histology, age at time of diagnosis (AAD)

- Of these 119 subjects, 29 (24.4%) were diagnosed with osteosarcoma, 18 (15.0%) with leiomyosarcoma, 12 (10.3%) with rhabdomyosarcoma and 9 cases (7.6%) of other sarcomas.
- Median AAD for all sarcoma subtypes was 28 years (interquartile range 18-46).
- Most notably, we found that, of the 9 osteosarcomas that had been diagnosed, 4 were located in either mandible or maxilla (figure 1).
- Of the 12 rhabdomyosarcomas that had been diagnosed, 6 cases were located in either extremities or muscular tissue.
- Of the 10 leiomyosarcomas that had been diagnosed, 8 cases were located in the gastrointestinal tract.
- Of the 30 sarcoma NOS that had been diagnosed, 18 cases were located in the extremities and 10 cases were located in the soft tissue of the body.

Sarcomas
- A total of 29 sarcomas was diagnosed in 28 patients.
- Osteosarcoma was most frequently diagnosed with 9 cases, followed by rhabdomyosarcoma with 6 cases.
- The median AAD for these two subtypes were 18 (11-41) and 5 (2-44), respectively. Median AAD for all sarcomas was 30 (interquartile range 18-46).
- Most notably, we found that, of the 9 osteosarcomas that had been diagnosed, 4 were located in either mandible or maxilla (figure 1).

CONCLUSIONS

We found a high incidence of osteosarcomas of the jaw at a relatively young age in the national screening cohort of TP53 mutation carriers in the Netherlands. Several case reports suggest a connection between LFS and this rare location for osteosarcoma, although a series as seen in our screening cohort has not been reported yet. Further exploration of associations between TP53 genotype and phenotypic features, such as sarcoma subtypes and their location, requires international collaboration with larger LFS cohorts.

Table 1. Incidence of sarcoma subtypes in Dutch TP53 germline mutation carriers.

<table>
<thead>
<tr>
<th>Sarcoma subtypes</th>
<th>Number of patients (n)</th>
<th>In males, n (%)</th>
<th>Median AAD, years (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteosarcoma</td>
<td>29 (24.4)</td>
<td>28 (18-46)</td>
<td>28 (11-41)</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>6 (58.0)</td>
<td>5 (2-44)</td>
<td>5 (2-44)</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>5 (58.0)</td>
<td>3 (60.0)</td>
<td>57 (27-71)</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>2 (66.7)</td>
<td>1 (100)</td>
<td>40 (26-53)</td>
</tr>
<tr>
<td>Other STS</td>
<td>4 (33.3)</td>
<td>3 (0.0)</td>
<td>36 (22-72)</td>
</tr>
<tr>
<td>Sarcoma NOS</td>
<td>4 (100.0)</td>
<td>0 (0.0)</td>
<td>47 (46-47)</td>
</tr>
</tbody>
</table>

Figure 1. Sarcoma subtypes and their locations. Total amount of sarcomas is 29. Other sarcomas consisted of two pleomorphic sarcomas of the skin and one spindle cell sarcoma of the foot.