Sarcomas: collaborative expertise drives major advances in research and care

Sarcomas are rare, complex and heterogeneous mesenchymal cancers. They account for 1% of cancers in adults and less than 10% in children. Overall, there are 4,000 to 5,000 new cases every year in France. Institut Curie is a national center of expertise in sarcoma research and management, and has been a driving force in improving patient survival.

A sarcoma is a rare cancerous tumor that forms at the expense of bone and soft tissue (connective, adipose, muscular, vascular, fibrous...). They can occur anywhere in the body (55% in the limbs, 45% in the central regions of the trunk and abdomen, and 5% in the head and neck), in both children and adults. *"Not only are sarcomas uncommon, but they also include more than a hundred different cancers in adult patients,"* notes **Dr. Sarah Watson, medical oncologist and researcher at Institut Curie.** *"Under these conditions, a non-specialist doctor will find it extremely difficult to make the right diagnosis of such a rare and poorly understood pathology. This is why, as soon as there is a suspicion of sarcoma and before any therapeutic procedure, it is essential to refer patients to a dedicated expert center in theNETSARC+ network, of which Institut Curie is a member, for diagnostic workup and therapeutic management."* **Analysis[4] of NETSARC+ results after 10 years of existence demonstrates the relevance of this recommendation, with an increase in patient survival[5],** as presented at the European Society for Medical Oncology (ESMO) congress in 2022.

The benefits of an expert center such as Institut Curie for multidisciplinary management of sarcoma patients

As one of France's leading sarcoma expert centers, Institut Curie boasts a comprehensive technical platform and offers a dedicated diagnostic pathway (CUSTOM) to support patients presenting with a soft tissue mass of undetermined etiology. This pathway is based on a medical imaging consultation combining clinical examination, analysis of radiological examinations, and biopsy if necessary, leading to anatomopathological and molecular biological analysis. **A recent study[6] by Institut Curie showed that a simple percutaneous biopsy of retroperitoneal tumors prior to any treatment enabled the diagnosis to be clarified in 98% of cases, so that the therapeutic strategy could be adapted** (possible preoperative treatment and surgical modalities). All this information is discussed at the "Sarcoma" multidisciplinary consultation meeting at Institut Curie. **This ensures that the patient receives the right diagnosis, and is already in the right circuit to benefit from an appropriate therapeutic strategy.** When sarcomas require surgery, it is performed by experienced surgeons, bearing in mind that these tumors can measure 30 centimetres and weigh several kilograms. If surgery is poorly performed, the chances of survival without recurrence are reduced. **Institut Curie teams have also shown that surgery in an expert center improves patients' prognosis. Another strength of Institut Curie is that it enables patients to take part in clinical trials, giving them access to the latest therapeutic innovations. What's more, a support team dedicated to the care of patients with advanced sarcomas collaborates with the whole team.**

Pooling Institut Curie expertise to reduce treatment costs

[4] Sylvie Bonvalot et al. *Survival benefit of the surgical management of retroperitoneal sarcoma in a reference center: a nationwide study of the French sarcoma group from the NetSarc database*. Ann Surg Oncol 2019 Jul;26(7):2286e93.

[5] *Jean-Yves Blay et al., Improved nationwide survival of sarcoma patients 10 years after establishment of the NETSARC+ reference center network,* Annals of Oncology 33, S1145-S1146, en cours.

[6] Walter Nardi et al., Diagnostic accuracy and safety of percutaneous core needle biopsy of retroperitoneal tumours., Eur J Surg Oncol. 2023 Nov 30;50(1):107298.

As an expert center for sarcoma patients, Institut Curie has coordinated "*a French national clinical and radiological follow-up study of desmoid tumors, which are soft tissue tumors characterized by a proliferation of fibroblastic cells associated with collagen production. These tumors are locally aggressive and invasive*", explains **Prof. Sylvie Bonvalot, a surgical oncologist specializing in soft tissue sarcomas at Institut Curie.** *"In the study, patients underwent MRI scans at 1, 3, 6, 9 and 12 months, then every 6 months for 3 years*[7]*. Only tumors shown to be progressive were treated."* **The study showed that half the tumours stabilized over the months, or even regressed spontaneously. This is beneficial for patients, as it shows that heavy treatment need not be systematic for this condition.**

A collaborative organization conducive to the discovery of new treatments

The expert center's resources also enable us to make available study aids for research: X-rays, biopsies, samples... Highly applied research, with patient consent of course, to track down the origin of sarcomas, better adapt therapeutic strategies and find new treatments. In addition, I**nstitut Curie collaborations are prolific, benefiting research advances.** *"Institut Curie's "Chemical Biology" team led by Dr. Raphaël Rodriguez studies the metabolism of metals and in particular iron in cancer cells,"* emphasizes Dr. Sarah Watson. *"Knowing about his research led me to believe that this pathway could be of potential interest in certain mesenchymal tumors."* A collaboration therefore arose between the two teams **to study iron metabolism in these tumors, demonstrating that iron plays a crucial role in their proliferation. What's more, the molecules developed by the Chemical Biology team appear to be particularly effective in destroying diseased cells.** *"To go even further, a multi-disciplinary project is currently being set up, involving radiologists from Institut Curie as well, to quantify iron from MRI images and predict the evolution of the disease. The idea is then to launch a national clinical trial within the Groupe Sarcome Français ."*

[7] Sylvie Bonvalot et al., *Initial Active Surveillance Strategy for Patients with Peripheral Sporadic Primary Desmoid-Type Fibromatosis: A Multicentric Phase II Observational Trial*, Annals of Surgical Oncology (2023).

Children's sarcomas: impressive recent progress

In addition to adult sarcomas, Institut Curie is also interested in children's sarcomas. *"Whether in terms of research or clinical management, situations vary according to age,"* admits **Dr. Olivier Delattre, pediatrician, Inserm research director and director of Institut Curie's SIREDO oncology center**[8]."*Bone tissue sarcomas appear in adolescence, whereas soft tissue sarcomas are seen in very young children, sometimes infants.* Children are referred to specialized pediatric facilities, such as Necker or Robert Debré hospitals. If sarcoma is suspected, they enter the CUSTOM program at Institut Curie to undergo the necessary tests as quickly as possible. ***"We are fortunate to have a dedicated unit for the molecular analysis of sarcomas, enabling us to make a precise diagnosis,"* enthuses Dr. Olivier Delattre.** *Surgery is not immediate afterwards, unlike in adults. Children undergo chemotherapy first, to reduce the tumor mass as much as possible and thus facilitate the surgical procedure in pediatric hospitals."*

For many years, therapeutic strategies for childhood sarcomas have evolved little. In recent years, however, they have progressed enormously, particularly in the field of targeted treatments. *Let's take the example of TRK-fused childhood sarcomas, which present a very specific molecular anomaly that activates the TRK receptor," explains Dr. Olivier Delattre. The development of a TRK receptor inhibitor (larotrectinib) has produced spectacular results in young patients."*[9] More recently, Dr. Olivier Delattre's team has highlighted the expression of highly specific genes in Ewing's sarcoma and certain other pediatric sarcomas[10]. *"The existence of these genetic mutations opens up the possibility of immunotherapies targeting tumor-specific proteins. We are collaborating with immunologists at the Institut to see whether these proteins represent relevant therapeutic targets for the development of immunotherapies. This breakthrough demonstrates once again the extent to which multidisciplinary collaboration at Institut Curie is a major asset for research", concludes Olivier Delattre.* This project is supported by Inca (*Institut National du Cancer*) and the European Fight Kids Cancer program.

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[8] SIREDO "Care, Innovation, Research in pediatric, adolescent and young adult oncology"

[9] Cancers pédiatriques : l'expertise de l'Institut Curie sur le devant de la scène internationale | Institut Curie

[10] Julien Vibert et al., ***Oncogenic chimeric transcription factors drive tumor-specific transcription, processing, and translation of silent genomic regions***, *Molecular Cell (2022).*