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Molecular Alterations in Pediatric Solid Tumors

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Section snippets

Key points

- Extracranial pediatric solid tumors exclude hematologic malignancies and central nervous system tumors....
- Pediatric solid tumors typically have a simpler molecular signature than their adult counterparts, with many harboring a single genetic alteration, often a gene fusion....
- Clinically significant molecular alterations in pediatric solid tumors are diagnostic, prognostic, or predictive of response to targeted therapy....
- Next-generation sequencing panels are increasingly being used in the evaluation of...

...

...

Overview

Malignant tumors in infancy, childhood, and adolescence can be divided into 3 broad groups: hematologic (leukemias, lymphomas, other), central nervous system tumors (brain and spinal cord), and extracranial solid tumors. Although most extracranial pediatric solid tumors (PSTs) are rare individually; together, they account for nearly 40% of all childhood cancers.[1,2] PSTs can be further subdivided into mesenchyme-derived tumors that occur primarily in bone and soft tissue and predominantly…

Categorization of pediatric extracranial solid tumors

There are several ways to categorize pediatric extracranial solid tumors (PSTs), which essentially represent a collection of rare tumors. For the following description of molecular alterations, we have subdivided PSTs into 2 major groups: tumors of bone and soft tissue and those arising from other organs.

Most PSTs arising in bone and soft tissue are sarcomas that exhibit mesenchymal differentiation, although many also include evidence of epithelial differentiation morphologically and with an…

Molecular alterations in pediatric bone and soft tissue tumors

Key molecular alterations in pediatric bone and soft tissue tumors are summarized in Table 1. Many of these alterations are included in the National Comprehensive Cancer Network guidelines for the diagnosis, prognosis, and selection of targeted therapies.[13]…

Molecular alterations in organ-based solid tumors

Key molecular alterations in nonbone and soft tissue PSTs are summarized in Table 2….

Differences from adult solid tumors

As demonstrated in Table 1, Table 2, PSTs encompass a heterogeneous group of tumors, many of which are individually rare or exclusive to childhood, such that a comparison between these tumors and their adult counterparts is challenging. Despite this heterogeneity, there are several notable differences between solid tumors in pediatric patients and those occurring in adulthood, including the following.

- *Tissue of origin:* In adulthood, the majority of solid tumors are carcinomas of epithelial…

…

Tumor predisposition syndromes in pediatric solid tumors

Children with cancer have a high prior probability of having a germline cancer predisposition, with more than 10% having an identifiable syndrome.148, 149, 150 A notable example is DICER1 tumor predisposition syndrome, first associated with pleuropulmonary blastoma and now with a several tumor types distributed throughout the body (Fig. 3).[95,130,133,159] Bone and soft tissue PSTs occur less commonly in the context of a tumor predisposition syndrome, with the notable exceptions of Gardner…

Molecular techniques

Molecular techniques are rapidly evolving. The selection of which molecular techniques to incorporate into a clinical practice is complex. Considerations include clinical usefulness, efficient use of scant tissue, assay availability, cost, and reimbursement. An overview of some conventional molecular and NGS techniques are provided elsewhere in this article….

Conventional molecular techniques

Conventional molecular techniques remain a mainstay of clinical practice (Table4). Targeted analyses including fluorescence insitu hybridization and single gene assays are cost effective, if limited in scope.…

Use of next-generation sequencing–based molecular assays in pediatric solid tumors

NGS refers to a variety of platforms that use massively parallel, high-throughput sequencing to provide simultaneous reads of million or billions of RNA and/or DNA strands.[181] Many NGS-based molecular assays have been developed in recent years for use in solid tumors that allow the simultaneous assessment of some or all of the following: sequence variants, insertions and/or deletions, copy number alterations, and gene fusions. Owing to its ability to interrogate multiple genes and alteration…

Clinics care points

- How well are the molecular alterations in PSTs covered by the assay?
  - Many are specific to pediatric patients and not routinely included on many adult-based assays.…

  …
- How much priority is given to fusions on the assay?
  - Coverage of introns takes up a lot of sequencing space on a DNA panel, such that rare pediatric fusions may not be prioritized. The addition of RNA-based fusion detection may be considered.…

  …
- How are fusions reported?
  - For some PSTs, the specific fusion partner is of diagnostic, prognostic, …

  …

…

Emerging concepts

The traditional practice of surgical pathology has been to use diagnostic categories that are based on the histomorphology and clinical characteristics of each tumor. As molecular techniques are increasingly integrated into clinical practice, the genomic associations are being incorporated into diagnostic categorization. This shift toward molecularly defined diagnoses has already been evident in both hematologic malignancies and central nervous system tumors.[183,184] New diagnostic entities are…

Summary

We provide a review of the clinically actionable molecular alterations in PSTs occurring outside of the central nervous system. These entities include molecular alterations with diagnostic or prognostic significance, those that predict response to targeted therapies, or those that are associated with a tumor predisposition. PSTs have unique clinical, epidemiologic, and molecular features in comparison with their adult counterparts, notably simpler genetic signatures, and a greater proportion of …

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First page preview

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KEYWORDS

• Pediatric pathology • Molecular • Solid tumors • Soft tissue and bone tumors

KEY POINTS

- Extracranial pediatric solid tumors exclude hematologic malignancies and central nervous system tumors.
- Pediatric solid tumors typically have a simpler molecular signature than their adult counterparts, with many harboring a single genetic alteration, often a gene fusion.
- Clinically significant molecular alterations in pediatric solid tumors are diagnostic, prognostic, or predictive of response to targeted therapy.
- Next-generation sequencing panels are increasingly being used in the evaluation of pediatric solid tumors and allow simultaneous assessment of a wide variety of gene fusions, sequence variants, and copy number alterations.
- Children with cancer have a high probability of having a germline cancer predisposition syndrome.

OVERVIEW

Malignant tumors in infancy, childhood, and adolescence can be divided into 3 broad groups: hematologic (leukemias, lymphomas, other), central nervous system tumors (brain and spinal cord), and extracranial solid tumors. Although most extracranial pediatric solid tumors (PSTs) are rare individually; together, they account for nearly 40% of all childhood cancers.[1,2] PSTs can be further subdivided into mesenchyme-derived tumors that occur primarily in bone and soft tissue and predominantly epithelial tumors that occur in other organs.

In adulthood, the vast majority of solid tumors are carcinomas of epithelial origin.[3] Carcinogenesis often follows via a well-characterized stepwise progression: from

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