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Increased survival of children with solid tumours: how did we get there and how to keep the success going?

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Abstract

Survival after childhood cancer has dramatically increased in the last 3 to 4 decades. Among extracranial tumours, Wilms tumours and other less common kidney tumours have the best results, but treatment of neuroblastoma, often disseminated at diagnosis, is still extremely challenging. How did survival of solid tumours in childhood increase from around 30% in the 1970s to 70–90% today? This is the result of a multidisciplinary effort and access to improved diagnostic techniques and treatment modalities. This article focuses on the role of imaging in this positive evolution and particularly, how imaging will contribute to keep the survival curves improving. Radiologists and other imaging experts retain a key position before diagnosis and during and after treatment. Investigations before diagnosis are key to further investigations and referral with no delay. The first investigations will most often involve radiologists through radiography or ultrasonography, according to tumour site. The description of these first observations and particularly the conclusion and its wording are crucial to the subsequent events leading to diagnosis. In imaging at diagnosis, the aim is to obtain a precise description of the primary tumour and its local spread as soon as possible. The choice of technique depends on local conditions but may include ultrasonography, computed tomography (CT)/magnetic resonance imaging (MRI) scanning, scintigraphies (bone, meta-iodobenzylguanidine (MIBG), octreotide), or fluorodeoxyglucose (FDG)-positron emission tomography (PET), combined with low dose CT or MRI scanning. CT scan and chest radiography are recommended for investigating the presence of lung metastases. There is no infiltrate too small to be a metastasis. Overall there is no specific imaging criterion. The pathologists hold this diagnostic key. Tumour response is evaluated during and after preoperative chemotherapy using techniques and measurements comparable with those used at diagnosis. Following evaluation of tumour response, additional investigations may be needed to define the resectability of the tumour, combining different imaging techniques, e.g. CT scanning and/or MRI angiographies, ultrasound with Doppler. After tumour resection and particularly in the case of non-radical resection, imaging of the tumour residue is required as baseline for further surveillance and eventually planning of irradiation fields. How do we secure further improvement in treatment results for childhood cancer? Multidisciplinary teams, optimal logistics and continuous education are the best tools with focus on reduction in delay to diagnosis and improvement in the multidisciplinary forum allowing optimal therapeutic decisions.

Keywords: *Childhood cancer; solid tumours; diagnosis delay; recurrence; surveillance; needle biopsy.*

Introduction

Survival after childhood cancer has dramatically increased in the last 3–4 decades. This is true for haematologic malignancies with almost 90% survival after lymphoblastic leukaemia; Hodgkin lymphoma and non-Hodgkin lymphoma have similar good to very good prognosis. Survival after myeloblastic leukaemia recently crossed the 50% line for the first time. Among extra cranial tumours, Wilms tumours and other less common kidney tumours have the best results but treatment of neuroblastoma, often disseminated at diagnosis, is still extremely challenging (Fig. 1). How did survival of solid tumours in childhood increase from around 30% in the 1970s to 70–90% today?

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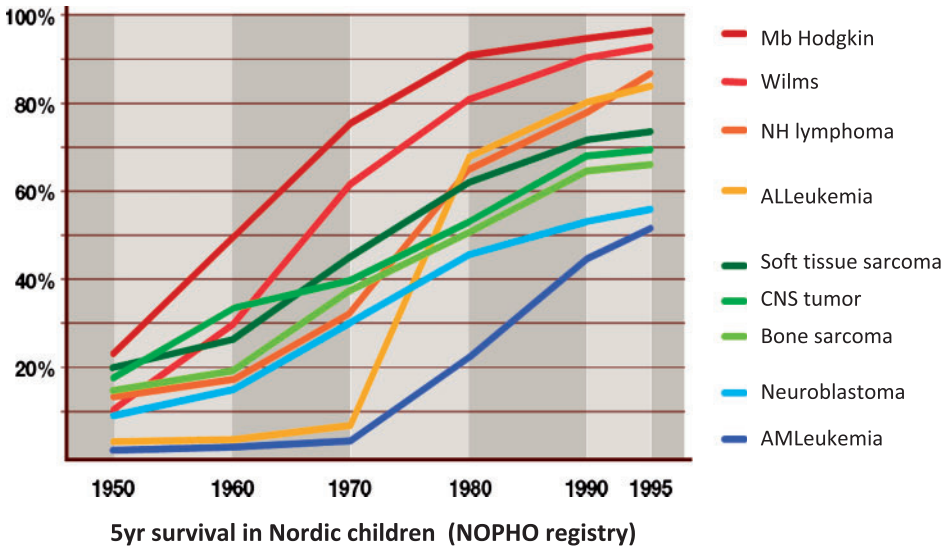

Figure 1 **Five-year survival in Nordic children (NOPHO registry).**

This is the result of a multidisciplinary effort and access to improved diagnostic techniques and treatment modalities. The increased survival after Wilms tumour is a good example of this evolution: with more precise diagnosis and evaluation of tumour extension, improved anaesthetics and better surgery in the 1970s; the use of radiotherapy for residual disease along with the introduction of low toxic chemotherapy, follow-up and diagnosis of relapses, local or distant, with a possibility of rescue and long-term survival in 2nd remission in the 1990s; reduction of treatment burden and particularly restricted use of radiotherapy with careful monitoring of its consequences for the last 10–20 years[1].

The focus of this article is the role of imaging in this positive evolution and particularly how imaging will contribute to keep the survival curves improving. There are challenges, controversies and yet unanswered questions. The treatment of solid tumours in children requires the participation of a large number of specialties, each playing a crucial role in the end result. The coordinating role is most often played by paediatric oncologists or by surgeons in the early phase of diagnosis. The radiologists and other imaging experts retain a key position before diagnosis and during and after treatment. The following imaging time points are discussed: before diagnosis; at diagnosis (primary tumour and extent of disease); evaluation of tumour response during treatment; end of treatment; follow-up (diagnosis of relapse, local or distant).

Before diagnosis: key to further investigations and referral with no delay

In the presence of symptoms and after contact with a general practitioner or an emergency unit, the first investigations will most often involve radiologists through radiography or ultrasonography, according to tumour site. The description of these first observations and particularly the conclusion and its wording are essential for the following events leading to diagnosis. Diagnosis delay is known to be much longer for bone tumours than for soft tissue tumours[2,3], suggesting that bone radiographs are not always well interpreted or that the observation by the radiologist of bone abnormalities suspicious of malignancy is not communicated further. Furthermore, discrete bone changes can seem benign at an early stage and thus be overlooked unless magnetic resonance imaging (MRI) is performed. Bone lesions which look malignant also require to be further investigated by MRI, with no delay. The conclusion of the radiologist plays a crucial role in the timing of the MRI to delay in diagnosis and treatment. After a description of observed anomalies, good examples could be: “If the patient has had a relevant trauma, these changes could represent sequelae after a fracture. In the absence of trauma the patient needs further investigations” or “Osteolytic changes lateral in the distal part of the femur. Adjacent to this abnormality, inhomogeneous sclerosing as well as swelling of the soft tissues is noted. These changes are suspicious for neoplasia.” These comments can seem like a normal daily occurrence to expert radiologists, but experience from daily life shows that they can have a very significant impact on patient care.

In contrast, the finding of a process suspicious for tumour should lead to speedier further investigations at least in children and young adults. Enlarged lymph nodes, where viral infections can complicate the diagnostic process, are more challenging. In these cases, exchange of clinical information in the framework of a multidisciplinary team will help guide the appropriate clinical pathway (biopsy or observation).

Imaging at diagnosis

Sedation or general anaesthesia

A newly admitted child up to around 6 years of age requires sedation or general anaesthesia for a number of investigations. When there are good possibilities to observe the child using a short procedure, e.g. computed tomography (CT) scanning or scintigraphy, sedation can be a good choice. MRI and positron emission tomography (PET) scans are quite timely and most often require general anaesthesia. The child will usually have to undergo a number of procedures in a few days, hence it is extremely important to coordinate and schedule the investigations to spare general anaesthesia and save time.

Investigation of the primary tumour

The aim is to obtain a precise description of the primary tumour and its local spread, as soon as possible. That can mean delaying an investigation in order to combine it with another and get more information at once. The available techniques are:

- Ultrasound
- CT scanning
- MRI scanning
- Scintigraphy (bone, meta-iodobenzylguanidine (MIBG), octreotide) or fluorodeoxyglucose (FDG)-PET, combined with low dose CT or MRI scanning.

CT scans have been used in children since the mid-1970s, first for intracranial processes but soon after for thoracic and abdominal tumours as well[4]. MRI was introduced for children in the early 1980s, again first for studies of the brain and soon after for chest, abdomen and extremities. These techniques have been compared and their pros and cons well described in different clinical situations[5–7]. Imaging techniques have grown in number, but even more in the quantity and quality of information they offer.

The choice of techniques will depend on local conditions such as availability of MRI expertise and of general anaesthesia for MRI, the site of the primary tumour and whether a chest CT scan is necessary for lung metastases. You also need to plan for tumour evaluation under treatment, and this is best done using the same technique.

This dilemma is well expressed in one of many treatment protocols for solid tumours in children: "First locoregional evaluation should be made with MRI. The choice between CT and MR depends also on local availability." These protocols also provide detailed radiologic guidelines and technical recommendations, e.g. for CT scanning or MRI scanning according to the tumour site and extension profile.

The evaluation of lung lesions

CT scan and chest radiographs are recommended for investigation of the presence of lung metastases at diagnosis. CT scan can be a particular challenge in small children because general anaesthesia causes laminar atelectases of the basal areas of the lungs, which might cover for basal lung infiltrates representing metastases[8,9]. If possible, sedation is preferred for a short CT scan and if anaesthesia is necessary, lungs should be scanned first (Fig. 2A,B).

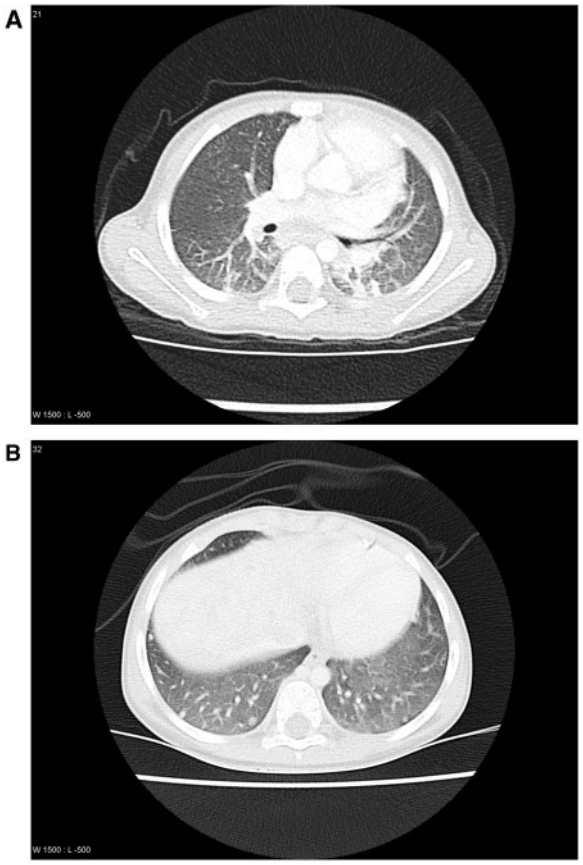

Figure 2 **CT scan of the chest in a 2-year-old girl under general anaesthesia (a), repeated 2 weeks later under sedation (b).**

Lung infiltrates: metastases or not?

There is no infiltrate too small to be a metastasis. Too small for the thoracic surgeon? Then it can be observed and if it grows a little bigger, it can be resected and evaluated histologically (Fig. 3A,B). In some protocols, it is agreed that one pulmonary/pleural nodule of 1 cm, or lesions >0.5 cm in more than one site, are considered evidence of pulmonary metastasis, as long as there is no other clear medical explanation for these lesions (e.g. Euro Ewing 99). These criteria are modified in some protocols considering nodules smaller than 5 mm as micrometastases and not equivalent to pulmonary metastatic disease (e.g. EpSSG RMS, 2005). There is

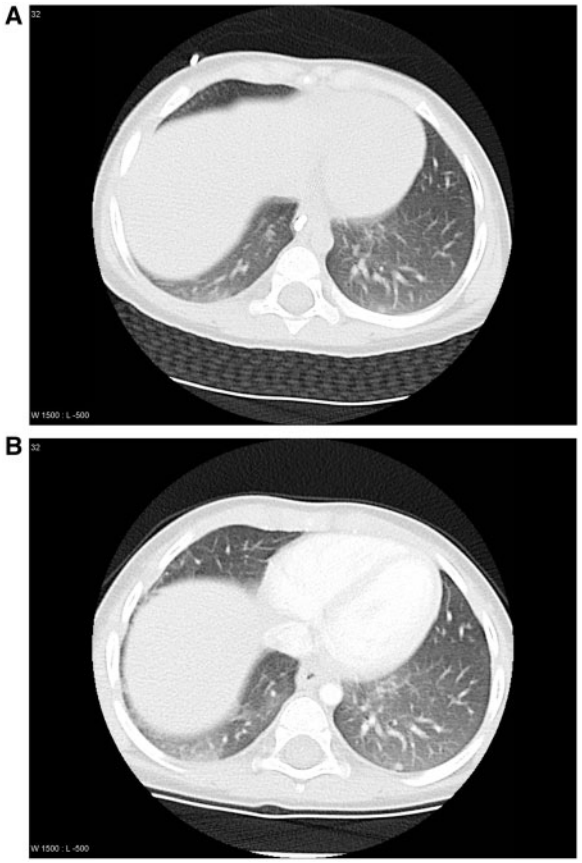

Figure 3 **Basal nodular lung infiltrate (a); progression after 2 months observation (b).**

no specific radiologic criterion and ultimately the pathologists hold this diagnostic key[10].

Evaluation of tumour response

Three measurements of diameter (sagittal, coronal and axial) are recommended in most protocols for solid tumours in children. One protocol plans for simultaneous registration of the maximal unidimensional diameter following RECIST guidelines. The tumour volume is calculated as follows: $V = 0.52 \times a \times b \times c$ in cm^3. Tumour response is evaluated during and after preoperative chemotherapy using the same technique and measurements as at diagnosis.

For the pathologist's diagnostic key, imaging-guided core biopsy or Tru-cut biopsy are required. Ultrasound or CT scan-guided core needle biopsy (18 or 16 gauge needles (1.2 or 1.6 mm) should be used. There is a minimal risk of contamination of the needle channel, which must be considered when planning the biopsy track. Fine-needle aspiration (22 gauge, 0.7 mm) is not recommended for diagnosis but may be used to provide additional cellular material for genetic examinations (EpSSG RMS 2005, unpublished).

Preoperative evaluation of tumour resectability

Following evaluation of tumour response, additional investigations may be needed to define the resectability of the tumour, combining different imaging techniques, e.g. CT and/or MRI angiography[11], ultrasound with Doppler. After tumour resection and particularly in the case of non-radical resection, imaging of the tumour residue is required as baseline for further surveillance and eventually planning of irradiation fields.

Follow-up after completion of treatment

Recommendations for surveillance for tumour recurrence are included in most protocols. In addition to clinical examinations, the following investigations can be included at increasing time intervals from 2–3 months to a year:

- Ultrasound
- Chest radiographs
- Radiographs of the primary area
- CT scanning
- MRI of the primary tumour site

The choice and combination of investigations is adjusted based on the tumour site, histology, and status at the end of treatment, with or without residual tumour.

Follow-up programs also include radiologic investigations of treatment sequelae, such as prostheses or other health problems, pulmonary or cardiologic, and screening for secondary malignancies, e.g. ultrasound of thyroid or mammography following irradiation.

How do we secure further improvement of treatment results for childhood cancer?

Improvement in treatment results requires multidisciplinary teams, with respect and good communication, optimal logistics and continuous education with focus on:

- Reduction of delay in diagnosis
- Improved multidisciplinary forum for optimal therapeutic decisions.

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