Whole lung irradiation in solid paediatric tumours: an indication to review?☆

Irradiación pulmonar total en los tumores sólidos pediátricos: ¿una indicación que ha de revisarse?

To the Editor:

The treatment of lung metastases of solid paediatric tumours and its impact on survival has been a controversial topic. The main studies on the subject have gathered data from patients with a variety of tumours such as Wilms' tumour, Ewing sarcoma, rhabdomyosarcoma or synovial sarcoma. Many have focused on a specific type of tumour, without predicting significant differences among them. Moreover, whole lung irradiation (WLI) has been integrated in current international protocols despite the lack of evidence on its impact on overall survival (OS).

We conducted a retrospective study in a sample of 24 children with lung metastases treated between 2000 and 2017, of who 18 received WLI. We analysed clinical characteristics (Table 1), the outcomes of lung metastases, the response to chemotherapy or irradiation, the time to relapse, radiation doses and dose fractionation, and survival outcomes. Our objective was to establish the benefits of WLI in patients that received prophylactic irradiation and patients that received radical radiotherapy (Table 2).

Of the 24 children under study, 18 had lung metastases at diagnosis, and 6 at the time of recurrence; the metastases were bilateral in 21. After chemotherapy (CTX), 8 patients exhibited a complete response (CR), 8 a partial response (PR), and the remaining 8 patients, disease progression or stabilization. Six children underwent surgery to remove the lung metastases. Prophylactic WLI was prescribed to 7 patients. The median dose was 16 Gy (range, 14.4-20 Gy). There was only 1 case of toxicity, corresponding to a patient that developed symptomatic pneumonitis.

Six patients did not receive WLI, of who 5 underwent surgery and 1 did not. Only 8 patients achieved a CR after WLI, 6 in the prophylactic WLI group and 2 in the radical WLI group. One patient exhibited pulmonary disease progression after prophylactic WLI. Of the 11 patients that received radical WLI, 7 exhibited pulmonary disease progression during the follow-up. With a median follow-up of 39 months, the 3-year overall survival of the total sample was 73% (89% of the prophylactic WLI group, and 63% of the radical WLI group). Factors that appeared to be associated with a poorer prognosis, but which were not statistically significant, were the presence of metastases at diagnosis, absence of a CR after chemotherapy, or not meeting the criteria for indication of lung surgery.

These data, consistent with other retrospective series in the literature, question the use of WLI in patients

Table 1 Clinical characteristics of studied patients.

Variables	*n*	%
Number of patients	24	
Sex		
Male/female	17/7	
Histological type		
Wilms tumour	4	16.7
Rhabdomyosarcoma	3	12.5
Ewing's sarcoma	13	54.2
Synovial sarcoma	2	8.3
Undifferentiated sarcoma	2	8.3
Location		
Pelvis	10	41.7
Genital	2	8.3
Lower extremity	4	16.7
Unilateral abdomen	3	12.5
Bilateral abdomen	1	4.2
Head and Neck	2	8.3
Thorax	1	4.2
Spine	1	4.2
Stage		
I	3	12.5
II	3	12.5
III	0	0
IV	17	70.8
V	1	4.2
Number of lung metastases		
1	2	8.3
3–5	3	12.5
>6	19	79.2
Location		
Unilateral	3	12.5
Bilateral	21	87.5
Surgery		
Yes	6	25
Lung response to CTX		
CR	8	33.3
PR	8	33.3
Stabilization	3	12.5
Progression	5	20.8
Dose fractionation (Gy)		
14.40–15	12	66.6
16–20	6	33.3
Lung response to RTX		
CR	8	44.4
PR	3	16.7
Stabilization	1	5.6
Progression	6	33.3
Relapse		
No relapse	8	37.5
Local	1	4.2
Pulmonary	2	8.3
Local and pulmonary	8	33.3
Extrapulmonary	4	16.7
Current status		
Alive with disease	8	33.3
Alive free of disease	7	29.2
Death related to disease	9	37.5

CR, complete response; CTX, chemotherapy; PR, partial response; RTX, radiotherapy.

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Table 2 Current indications in clinical trials of WLI.

Protocol	Wli indication
EUROEWING 2012	[•]Indicated in patients with pleural of pulmonary metastatic disease (R2 VAI and R2 IEVC) in both arms A and B, on completion of consolidation CTX (R2 VAI and R2 IEVC) • Doses: [o]<14 years: 15 Gy in 10 fractions o ≥14 years: 18 Gy in 12 fractions • Contraindication with CTX schemes containing busulfan-melfalan (any dose of RTX)
UMBRELLA SIOP-RTSG 2016	[•]WLI is not indicated in low-risk histology • In intermediate-risk histology: [o]Absence of CR of lung metastases in computed tomography after CTX (week 10 of postoperative chemotherapy) and/or surgery o Histological viable tumour after CTX and surgery in resected metastases o RTX should not be given if computed tomography shows CR at week 10 of postoperative chemotherapy • In high-risk histology cases of primary lung metastases regardless of the response to chemotherapy or surgical treatment • In lung relapses: [o]Always indicated when prior WLI has not been given (after surgery or CTX) o WLI cannot be used in case lung irradiation was used as first-line treatment o Consider SBRT in case of small-volume residual disease
EpSSG RMS 2005	[•]Recommended in case of 1 or more lung metastases (15 Gy in 10 fractions)

with lung metastases after CTX that are not eligible for surgery. The impact on local disease control and overall survival after WLI in patients with measurable lung disease is poor and, although the toxicity of radiotherapy (RTX) is low, the clinical benefits of WLI should be considered.

While prophylactic WLI has proven beneficial in terms of pulmonary disease-free survival (DFS), its influence in OS has not been studied so long. In a study in patients with inoperable metastases of nephroblastoma, Verschuur et al. found that the 5-years OS in the inoperable group was lower compared to survival in patients that underwent resection and received CTX (48% vs 92%; $P < .001$).[1] Dix et al. studied children with nephroblastoma and lung metastases treated with RTX, comparing children with a complete response after CTX that did not receive WLI and children with an intermediate response to CTX that received WLI. In the complete response group, the 4-year DFS and 4-years OS were 79.5% and 96.1%, respectively. In the intermediate response group, the 4-year DFS and OS were 88.5% and 95.4%, respectively.[2]

Roderberg et al. assessed the benefits of adding WLI to the management of children with lung metastases of rhabdomyosarcoma, and found that WLI was associated with a decrease in pulmonary recurrence ($P = .04$), but had no impact in OS (WLI, 47% vs no WLI, 30%).[3] In children with lung metastases of Ewing Sarcoma treated with RTX, Casey et al. described an improvement in the incidence of pulmonary recurrence, DFS and OS in patients treated with WLI and exclusive lung metastases compared to children with extrapulmonary disease, with a survival free of pulmonary disease of 45%.[4] Scobioala et al. analysed the role of WLI in children who had pulmonary recurrence and were rescued with surgery and/or CTX followed by WLI, describing a benefit in the 3-year-OS in patients that exhibited a CR compared to a partial response or stabilisation of the disease (65% vs. 53%; $P = .03$), an association that was not maintained in the 3-year DFS (54% vs. 49%; $P = .10$).[5]

Ongoing clinical trials in solid paediatric tumours (EuroEwing, Umbrella, EpSSG RMS 2005...) continue to include the indication for WLI, despite a lack of evidence of it having a positive impact on OS. Moreover, trial protocols do not adjust the dose of RTX prescribed for macroscopic disease or in case of lack of response to CTX. The only factor that is considered for adjustment of the RTX dose is age (15 Gy vs 18 Gy).

To date, no prospective studies have been published that attempt to clarify the indication of WLI in these patients. Aspects to be considered in the design of future clinical trials include performing surgery or delivering higher RTX doses in measurable metastases with stereotactic radiation therapy techniques and comparing outcomes in disease control and survival, with and without the use of WLI, in patients that are candidates for prophylaxis.

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Kangaroo care during the SARS-CoV-2 pandemic in Spain☆

El método canguro durante la pandemia por SARS-CoV-2 en España

To the editor:

The coronavirus disease 2019 (COVID-19) pandemic started in Wuhan (China) in December 2019. The novel coronavirus (SARS-CoV-2) spread rapidly through every country in the world, and in March 2020 the first case in a neonate was detected in Spain.[1]

In neonatal units, the practice of kangaroo care (KC) was affected in the first months of the pandemic due to the lack of robust evidence on the mechanisms of viral transmission and the potential impact on neonates.[2] For instance, to guarantee infant safety, the University Hospital of Padua (Italy) implemented screening of all neonates, parents and health care professionals in neonatal units, which achieved good outcomes even at times when the incidence was peaking.[3]

The aim of our study was to assess the impact of the SARS-CoV-2 pandemic on KC in neonatal units in Spain and identify possible opportunities for improvement in the context of the pandemic.

We conducted a cross-sectional, observational and descriptive study. We developed an ad hoc questionnaire that was distributed through social networks to professionals staffing neonatal units in Spain. The study focused on assessing the impact of the pandemic on KC and the opinions and perceptions of health care workers regarding the situation.

A total of 263 health care workers, with representation of every autonomous community in Spain, participated in the survey, the results of which are summarised in Table 1.

As would be expected, there was evidence of a decrease in the unrestricted practice of KC during the pandemic, from a frequency of 97% before the pandemic based on data published in 2020 by López et al[4] to 46% based on our findings. In addition, the proportion of units that offered unrestricted 24-hour access to parents decreased from 95.4% to 85.2%.[4]

At the international level, a similar study in the United States found a significant decrease in parental presence (from 85% to 53%) and parental participation in infant care (71% to 32%), leading the authors to conclude that restrictions had significantly limited the presence of families in neonatal units.[2]

Despite the low incidence of SARS-CoV-2 infection in neonates, as evinced by data from the Sociedad Española de Neonatología (Spanish Society of Neonatology),[1] the pandemic has brought significant changes in neonatal care delivery and practices, with a negative impact on practices in which there had been substantial progress.[5] In March 2020, as the pandemic emerged, uncertainty and the rapid spread of the virus led to the implementation of measures that restricted parental visits to neonatal units, with an impact on their active participation in infant care, including KC, and barring grandparents, siblings and other relatives that provided psychological and social support to the parents from the units.

These restrictive strategies meant to reduce the spread of the virus and protect neonates and health care workers carried different risks for infants and their families and were a source of additional concern for health care workers on account of their potential impact, as limiting developmental care practices could have a negative impact on parent-child bonding, the prevalence of breastfeeding and neurodevelopmental outcomes in preterm infants.[5,6]

The current global health crisis and constant changes in protocols and guidelines constitute a substantial professional and emotional challenge.[6] But as the data available to date suggest,[1–4] the risk of vertical transmission in the infant is very low. In addition, the benefits offered by KC, parent-child bonding and breastfeeding vastly exceed the risks associated with infection by SARS-CoV-2 in newborn infants.

After a very slow introduction of KC, which has taken more than 20 years in neonatal units in Spain, the pandemic has had a substantial negative impact on its practice. In only a few months, there has been a significant decrease in the practice of KC due to general restrictions on parental presence in neonatal units and specific restrictions on skin-to-skin contact that may have a negative impact on infants and their families. If there is uncertainty regarding potential

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