Minimising radiotherapy in children with rhabdomyosarcoma

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US and European paediatric oncologists are finally finding common ground over which patients need potentially damaging aggressive local treatment, and which can be spared.

The gap between Europe and North America on the treatment of young children with rhabdomyosarcoma may not be as wide as readers of recent papers in the *Journal of Clinical Oncology* might have suspected.

The main paper (JCO 23:2618-28) reported on the third study of the International Society of Paediatric Oncology (SIOP) on malignant mesenchymal tumours (MMT 89), which set out to improve outcomes for children with non-metastatic rhabdomyosarcoma and reduce systematic use of local therapy such as radiotherapy. It was accompanied by an editorial commentary from the US (pp2586–87), which explained the 'philosophical differences' that exist between the continents in relation to rhabdomyosarcoma management, predominantly focusing on the greater enthusiasm for local treatment in North America.

MMT 89 lead author Michael Stevens and James Anderson, a member of the US Intergroup Rhabdomyosarcoma Study Group (IRSG) IRS-IV investigation and co-author of the JCO editorial, are two of the main 'protagonists' in this philosophical debate. Yet while both agree that some differences still exist, they actually adopt positions much nearer to one other than the rhetoric would suggest.

"We're close", says Anderson, who is chair of the Department of Preventive and Societal Medicine at the University of Nebraska Medical School. "There's been a great deal of interaction and exchange of information over the last couple of years. It's my sense that the respective therapeutic approaches are moving closer, with the Europeans becoming somewhat more aggressive with local therapy than they have been in the past with some subsets of patients, and we in the US adopting less aggressive approaches for patient groups in whom the Europeans have shown success."

Meeting of minds

Stevens, CLIC Professor of Paediatric Oncology at the University of Bristol, UK, agrees. "We're moving towards meeting in the middle," he says. "There has been a move away from a uniform rule in North America that everyone gets radiotherapy, to a slightly more selective approach. They've taken on board our demonstration that some patients can be cured with less treatment than they might normally give, and we've looked critically at our own results and have made amendments to our strategies." The principle behind the MMT studies is to limit the use of local therapy as far as possible, particularly radiotherapy. The great majority of children with rhabdomyosarcoma are very young, yet radiotherapy historically has formed an important part of their treatment, bringing with it significant long-term effects.

The MMT 89 results in relation to overall survival, however, don't compare favourably to the US IRS-IV investigation, which featured early radiotherapy for several groups of patients, including the very young. "You can't deny that the results of the IRS-IV study look somewhat better than ours," Stevens concedes. "Their results are stunningly good for tumours of the orbit, with 100% survival claimed. We have had to accept that the MMT 89 experiment didn't work in its entirety and that some of the patients we tried to treat without radiotherapy actually do need it. We've consequently made modifications to our treatment strategies by introducing radiotherapy for more children on the basis of those results.

James Anderson (US): We've halved the radiotherapy for low-risk rhabdomyosarcoma patients on the basis of data from Europe

Michael Stevens (UK): We've introduced radiotherapy for more children, because the US results were better than ours

But the fundamental of the whole debate is – can you actually cure as many children without exposing them to more treatment than is necessary?"

Stevens accepts that the price of trying to answer this question can be high. "It brings major anxiety that some children who relapse may die because they weren't treated more aggressively in the first place," he says. "And those who don't die but are salvaged will require more treatment in the end than might otherwise have been necessary."

Treating for the long term

But keeping an eye on the long-term picture is enormously important, Stevens believes. "If we are going to create a population of young people who have survived cancer in childhood, we want to minimise the consequences of their experience of the disease and its treatment in adult life," he says. "One of the great difficulties of applying this general principle is that it is something you can talk about comfortably across a population, but find more difficult to do in relation to an individual child. But I know that if I have a two-year-old with a tumour of the orbit, I will do my best to treat him without exposure to radiotherapy if I can."

The position historically taken in North America is that it doesn't matter whether the child is two or eight – the majority still get radiotherapy and will receive treatment longer than similar patients in Europe. That approach is being softened, however, as Anderson explains.

"Patients with orbital rhabdomyosarcoma are emblematic of the difference in approach," he says. "In the US, we typically use local control as part of the initial therapy in an attempt to maximise the cure rate. The SIOP approach is directed towards attempting to minimise the late effects, recognising that they will observe high recurrence but with a very high salvage rate for those patients."

But Anderson too believes that the last couple of years have seen movement from both sides towards similar approaches. "Patients with alveolar histology tumours who were treated in the most-recently closed SIOP study received radiation as part of their initial therapy as a result of comparative analyses with the US experience," he says. "That's a case where, for a subset of patients, the Europeans have moved towards a more North American approach."
And the North Americans have reciprocated, Anderson states.

"We've recently opened a study for the treatment of low-risk rhabdomyosarcoma," he explains. "Until quite recently, the standard length of therapy in the US was just short of a year. In the new study, patients with low-risk disease have had their therapy cut to 24 weeks, largely because we know from European studies that similar patients treated for a very short time – 9-16 weeks – have done quite well. Those data gave us comfort in reducing the length of therapy."

Things have moved to the point where researchers from the two continents are considering creating a combined dataset and running some collaborative comparisons.

"We've begun discussions along those lines," Anderson confirms. "We both have an extensive historical database on the experience of treating children with rhabdomyosarcoma. The IRS-IV and MMT 89 studies were conducted almost contemporaneously, so the idea is that by assembling data from those studies in one place with variables defined in the same way, we can begin to make some formal comparisons."

While North America and Europe may be at loggerheads in some spheres, this looks to be one area where peace has broken out.