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Local control and sequelae in localised Ewing tumours of the spine: A French retrospective study

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KEYWORDS

Ewing Sarcoma Vertebra Non-metastatic Local control Sequelae **Abstract** *Objectives:* To evaluate both local outcome and sequelae of non-metastatic spinal Ewing tumours (EWT).

Patients and methods: A French cohort of patients ≤50 years with localised spinal EWT treated between 1988 and 2009, was analysed in regard to tumour characteristics (e.g. volume, vertebral compartment, spinal cord compression, paraspinal soft tissue invasion), local treatment modalities (surgery (S) and margin quality, radiotherapy (RT) dose), response to treatment (e.g. histological response to neoadjuvant chemotherapy (CT)), tumour local control (LC) and sequelae.

Results: Seventy-five patients treated in successive trials were evaluated for LC: SFOP-EW88 (n=14), SFOP-EW93 (n=17) and EuroEwing99 (n=44). Fifty-seven patients (79%) presented initial neurological compression and 69% had inaugural decompressive S. Local treatment modality was S + RT (n=50), RT alone (n=19) and S alone (n=6). Surgery was mainly intralesional (66%). Local recurrences had occurred in 19 patients (14 local, 5 locoregional) with a median interval of 25 months (1–50). After a 7 year median follow-up (1–22 years), the 5-year LC, relapse-free survival (RFS) and overall survival (OS) reached 78.0% (95%CI: 62.6–84.6), 57.0% (95%CI: 45.2–68.9) and 70.0% (95%CI: 59.1–81.0), respectively. Vertebral compartment involved was the only prognostic factor (5-year LC rate 100% versus 71% for favourable and unfavourable compartment, p < 0.03). Among 41 five-year survivors, we observed spinal curvature deformation (35%), growth retardation (28%), spinal reduction mobility (40%), spinal pain (25%) and neurological sequelae (32%) without any significant association with a particular local procedure.

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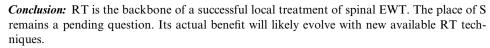
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1. Introduction

Ewing's tumour (EWT) is the second most common primary bone malignancy in childhood and adolescence. 10% of EWT are primarily located on the spine. Local control (LC) and survival rates are usually considered poorer than in other primary sites. 3,4 The presence of the spinal cord or *cauda equina* renders local treatments challenging. Both surgery (S) and radiotherapy (RT) have their limits and complications.

En bloc resection mortality rate may reach 8%.⁵ Post-operative complication incidence varies between 10% and 30% (including vascular, neurological, orthopaedic and infectious complications). Risk factors are multisegmental resections and double combined approaches (anterior and posterior approaches performed during the same operation by two surgeons).⁶ Margins have to be reduced to protect nervous and vascular structures, exposing patients at risk of incomplete resection and local recurrence, and justifying postoperative RT use.

Due to the dose-dependent risk of radiation-induced chronic, progressive, disabling and irreversible myelopathy, the dose focally received by the full-thickness of the spinal cord is usually limited to 45 Gy (1.8–2.0 Gy/day), which is significantly below the optimal dose recommended to treat EWT in other primary locations. RT may lead to spinal deformity, soft tissue fibrosis, contracture and an increased cumulative risk of second malignancies.

The aim of this study is to evaluate non-metastatic spinal EWT local treatment influence on LC and sequelae, and the associated prognostic factors.

2. Patients and methods

2.1. Population

We retrospectively studied previously untreated non-metastatic spinal EWT, in patients ≤50 years old, treated in France between 1988 and 2009, by two successive French therapeutic trials, the SFOP-EW88¹⁰ and EW93¹¹, and in the current European intergroup Euro-EWING99 trial (EE99; NCT00020566). Sacral tumours were excluded due to their specific issues. 13,14

Diagnostic, staging procedures and initial gross tumour volume (iGTV) calculation/estimation were previously described. 10,11

2.2. Treatments

The treatment outlines of these studies were comparable with induction chemotherapy (CT) followed by local

treatment and maintenance CT for a total duration of 10–12 months (Fig. 1). Prompt initial symptom-oriented surgery (decompressive surgery, dS) – usually laminectomy – was performed prior to any other treatment, when tumour induced symptomatic neurological compression.

Induction/neoadjuvant CT included cyclophosphamide + doxorubicine (×5 courses, French trials)^{10,11} or vincristine + ifosfamide + doxorubicine + etoposide (VIDE×6 courses, EE99).¹⁵

The local treatment was preferentially performed after induction CT, multidisciplinarily anticipated at diagnosis, not randomly assigned and modalities decided according to clinical characteristics (e.g. age, tumour location and size, response to CT), availability of surgical/RT resources, anticipated morbidity and patient preference.

S was recommended when radical resection was deemed achievable according to imaging-based staging. Radical procedures depended on tumour location/extension. Quality of the resection was independently reviewed by an expert orthopaedic surgeon in 73% of the operated patients (n = 41/56). Numbers given in the tables are based upon the review.

RT was recommended in all cases and performed after completion of induction CT or 2–4 weeks after the post-induction S. The recommended dose on the operative bed including healthy over- and underlying vertebrae was 44 Gy (1.8–2.0 Gy/day). In case of poor response to induction CT, microscopically incomplete resection or exclusive RT, the dose was increased up to 54 Gy below the *conus medullaris*. The maximal dose to the full-thickness of the spinal cord was ≤45 Gy. 3D-conformal RT planning with dose-volume histograms were recommended in EE99.

Maintenance CT was risk-stratified in EW93 and EE99 trials. ^{10,11} Due to its radiosensitiser effect, consolidation CT was delivered during RT without actinomycin and high dose CT (Busulfan/Melphalan) was not recommended when radiation fields were encompassing the spine.

2.3. Sequelae

Five year-activity, neurological and orthopaedic sequelae were evaluated by the referring physician among the 5-year survivors with a questionnaire. Fig. 3 shows the investigated parameters.

2.4. Statistical analysis

LC probabilities were calculated from the start of the first carcinologic-intended local treatment to the date of

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