Egyptian National Guidelines for Ewing Sarcoma

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Abbreviations

AYA (Adolescent and Young Adult)

BM (bone marrow)

COG (Children's Oncology Group)

CT (computed tomography)

FDG (fluorodeoxyglucose F18)

GCSF (granulocyte colony stimulating factor)

IHC (immunohistochemistry)

MRI (magnetic resonance imaging)

NCCN (National Comprehensive Cancer Network)

PET (positron emission tomography)

RT (radiation therapy)

Glossary:

Negative surgical margins: Minimal distance between the tumour and surgical margins is more than 2 mm. [(1)]

Positive surgical margins: Minimal distance between the tumour and surgical margins is 2 mm or less. [(1)]

Executive Summary:

This guidance provides a data-supported approach to the diagnosis, treatment, and follow up of paediatric patients diagnosed with Ewing sarcoma.

Recommendations	Strength Of recommendation
1-Work up for newly diagnosed Ewing Sarcoma	
Image guided biopsy with IHC is recommended.	Strong recommendation
Molecular studies are recommended as needed guided by expert opinion.	Conditional recommendation
Contrast enhanced MRI of the primary site is recommended.	Strong recommendation
We recommend PET/CT if available or CT chest and bone scan if PET/CT is unavailable.	Strong recommendation
Bone marrow biopsy is recommended if PET/CT is unavailable or positive uptake of bone marrow in PET/CT.	Strong recommendation
2- First line therapy for non-metastatic primary tumour (neoadjuvant/adjuvant)	
Multiagent chemotherapy for at least 9 weeks prior to local therapy is recommended (**interval compressed chemotherapy**). All patients are recommended to continue adjuvant chemotherapy after local control till 28 weeks.	Strong recommendation Strong recommendation
Preferred Regimen VDC/IE (Vincristine, doxorubicin and cyclophosphamide) alternating with (Ifosfamide and etoposide) every 2 weeks with GCSF for a total of 14 cycles.	Strong recommendation
Restage after neoadjuvant therapy before local control CT chest and contrast enhanced MRI of primary site are recommended.	Strong recommendation
Local Control Therapy for stable/improved disease following neoadjuvant therapy	
We recommend wide surgical excision and adjuvant chemotherapy. Radiotherapy is recommended if positive surgical margins.	Strong recommendation
Definitive radiotherapy and adjuvant chemotherapy are recommended for irresectable tumours.	Strong recommendation

3- First line therapy for metastatic disease at initial presentation	
Multiagent chemotherapy for at least 9 weeks prior to local therapy is recommended (**interval compressed chemotherapy**). *Preferred Regimen* VDC/IE (Vincristine, doxorubicin and cyclophosphamide) alternating with (Ifosfamide and etoposide) every 2 weeks with GCSF for a total of 14 cycles. All patients are recommended to continue adjuvant chemotherapy after local control till 28 weeks.	Strong recommendation
Local control for metastatic disease	
We recommend wide surgical excision and adjuvant chemotherapy. Radiotherapy is recommended if positive surgical margins.	Strong recommendation
Definitive radiotherapy and adjuvant chemotherapy are recommended for irresectable tumours.	Strong recommendation
Management of metastases	
For lung only metastases with partial response to neoadjuvant treatment, resection and whole lung irradiation are recommended.	Strong recommendation
For lung only metastases with complete response to neoadjuvant treatment, whole lung irradiation is recommended.	Strong recommendation
For bone metastases it is recommended to give radiotherapy to metastatic sites.	Strong recommendation
4- Radiotherapy	
Timing of RT For patients receiving radiation therapy only it is recommended to be delivered at the beginning of week 13 concurrently with chemotherapy.	Strong recommendation
If post-operative radiotherapy is recommended, consider starting at week 15 concurrently with chemotherapy starting on day 1 of the cycle as soon as possible after surgery.	Strong recommendation

Patients with recent cord compression are recommended to start emergency concurrent radiotherapy and chemotherapy starting from day 1 first cycle.	Strong recommendation
Concurrent chemotherapeutic agents Ifosfamide, etoposide, cyclophosphamide and vincristine should be given with radiotherapy. It is recommended to withhold doxorubicin with radiotherapy and re-institute after completion of radiation.	Strong recommendation
5- Treatment of recurrent/relapsed Ewing Sarcoma	
Chemotherapy Recommended chemotherapy combination • Irinotecan and temozolomide in 21-day interval cycles, Or • Ifosfamide, carboplatin and etoposide (if > 6 months).	Strong recommendation
Surgery Surgical resection of both local and metastatic sites (especially pulmonary) if feasible is recommended.	Strong recommendation
Radiotherapy Radiation is recommended either definitive or postoperative.	Strong recommendation
6- Surveillance – Follow up - for Ewing Sarcoma patients	
X-ray of the primary site is recommended every 4 months for the first 2 years and as clinically warranted.	Strong recommendation
CT chest every 4 months is the recommended chest imaging in the first 2 years. Chest X-ray is recommended for chest imaging in later years.	Strong recommendation
It is recommended to increase intervals of imaging of primary site and chest after 24 months and annually after 5 years (indefinitely).	Strong recommendation

Introduction

Ewing sarcoma is the second most common primary bone tumour in paediatric population, accounting for about 1% of all childhood cancers. This malignancy typically originates in the bones or the surrounding soft tissues and most frequently affects AYAs, with a common age range at diagnosis between 10 and 20 years. The incidence of Ewing sarcoma is notably higher among individuals of European and North African/Middle Eastern ancestry, making it a significant concern in these populations. Despite its rarity, Ewing sarcoma is known for its aggressive nature and the challenges it presents in treatment and management. (2)(3)

Scope of the Guideline:

These guidelines are developed to improve the quality of care for Ewing Sarcoma cancer patients Via providing a uniform standard of care across the country to help in early diagnosis and treatment for Ewing Sarcoma, with improved clinical outcomes. These guidelines cover primary diagnosis, treatment and follow-up of Ewing Sarcoma patients.

Target audience

Clinicians who are involved in the care and treatment of patients with Ewing Sarcoma, including paediatric oncologists, radiation oncologists, surgeons, radiologists, pathologists, and palliative care specialists.

Methodology

 A comprehensive search for guidelines was undertaken to identify the most relevant guidelines to consider for adaptation.

 inclusion/exclusion criteria followed in the search and retrieval of guidelines to be adapted:

- Selecting only evidence-based guidelines (guideline must include a report on systematic literature searches and explicit links between individual recommendations and their supporting evidence).
- Selecting only national and/or international guidelines.
- Specific range of dates for publication (using Guidelines published or

updated 2015 and later).

- Selecting peer reviewed publications only.
- Selecting guidelines written in English language.
- Excluding guidelines written by a single author not on behalf of an organization in order to be valid and comprehensive, a guideline ideally requires multidisciplinary input.
- Excluding guidelines published without references as the panel needs to know whether a thorough literature review was conducted and whether current evidence was used in the preparation of the recommendations.

 All retrieved Guidelines were screened and appraised using AGREE II instrument (www.agreetrust.org) by at least two members. the panel decided a cut-off points or rank the guidelines (any guideline scoring above 50% on the rigour dimension was retained)

The NCCN guidelines are the main source used while formulating the national guidelines for Ewing Sarcoma.

 Evidence assessment

According to WHO handbook for Guidelines we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess the quality of a body of evidence, develop and report recommendations. GRADE methods are used by WHO because these represent internationally agreed standards for making transparent recommendations. Detailed information on GRADE is available through the on the following sites:

. GRADE working group: http://www.gradeworkingroup.org

. GRADE online training modules: http://cebgrade.mcmaster.ca/

. GRADE profile software: http://ims.cochrane.org/revman/gradepro

Table 1: Quality of evidence in GRADE

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Quality level	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

GRADE: Grading of Recommendations Assessment, Development and Evaluation.

Table 2: Significance of the four levels of evidence

Quality	Definition	Implications
High	The guideline development group is very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change confidence in the estimate of effect
Moderate	The guideline development group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect	Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate
Very low	The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	Any estimate of effect is very uncertain

Table 3: Factors that determine How to upgrade or downgrade the quality of evidence

Downgrade in presence of	Upgrade in presence of
Study limitations -1 Serious limitations -2 Very serious limitations	Dose-response gradient +1 Evidence of a dose-response gradient
Consistency -1 Important inconsistency	Direction of plausible bias +1 All plausible confounders would have reduced the effect
Directness -1 Some uncertainty -2 Major uncertainty	Magnitude of the effect +1 Strong, no plausible confounders, consistent and direct evidence
Precision -1 Imprecise data	+2 Very strong, no major threats to validity and direct evidence
Reporting bias -1 High probability of reporting bias	

The strength of the recommendation

The strength of a recommendation communicates the importance of adherence to the recommendation:

Strong recommendations

With strong recommendations, the guideline communicates the message that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This means that in most situations the recommendation can be adopted as policy.

Conditional recommendations

These are made when there is greater uncertainty about the four factors above or if local adaptation must account for a greater variety in values and preferences, or when resource use makes the intervention suitable for some, but not for other locations. This means that there is a need for substantial debate and involvement of stakeholders before this recommendation can be

adopted as policy.

When not to make recommendations.

When there is lack of evidence on the effectiveness of an intervention, it may be appropriate not to make a recommendation.

Recommendations

1-Work up for newly diagnosed Ewing Sarcoma

Image guided biopsy with IHC is recommended.

strong recommendation, high quality level of evidence (systematic review and meta-analysis, comparative trial) [4][5]

Molecular studies are recommended as needed guided by expert opinion.

Conditional recommendation, low quality level of evidence (retrospective analysis) [6]

Contrast enhanced MRI of the primary site is recommended.

strong recommendation, high quality level of evidence (comparative trial) [5]

We recommend PET/CT if available or CT chest and bone scan if PET/CT is unavailable.

strong recommendation, high quality level of evidence (systematic review and meta-analysis) [4]

Bone marrow biopsy is recommended if PET/CT is unavailable or positive uptake of bone marrow in PET/CT.

strong recommendation, high quality evidence (systematic review) [7]

2- First line therapy for non-metastatic primary tumour (neoadjuvant/adjuvant)

Multiagent chemotherapy for at least 9 weeks prior to local therapy is recommended (**interval compressed chemotherapy**).

strong recommendation, high quality level of evidence (randomised trials) [8-13]

All patients are recommended to continue adjuvant chemotherapy after local control till 28 weeks.

strong recommendation, high quality level of evidence (randomised trials) [8-13]

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Preferred regimen

VDC/IE (Vincristine, doxorubicin and cyclophosphamide) alternating with (ifosfamide and etoposide) every 2 weeks with GCSF for a total of 14 cycles.

strong recommendation, high quality level of evidence (randomised trial) [13]

Restage after neoadjuvant therapy before local control

CT chest and contrast enhanced MRI of primary site are recommended.

strong recommendation, high quality level of evidence (COG report, randomised trial) [14][15]

Local Control Therapy for stable/improved disease following neoadjuvant therapy

We recommend wide surgical excision and adjuvant chemotherapy. Radiotherapy is recommended if positive surgical margins.

strong recommendation, high quality level of evidence (retrospective analysis, COG report, prospective study) [16][17][18]

Definitive radiotherapy and adjuvant chemotherapy are recommended for irresectable tumours.

strong recommendation, high quality level of evidence (retrospective analysis, COG report, prospective study) [16][17][18]

3- First line therapy for metastatic disease at initial presentation

Multiagent chemotherapy for at least 9 weeks prior to local therapy is recommended (**interval compressed chemotherapy**).

Preferred Regimen

VDC/IE (Vincristine, doxorubicin and cyclophosphamide) alternating with (ifosfamide and etoposide) every 2 weeks with GCSF for a total of 14 cycles.

All patients are recommended to continue adjuvant chemotherapy after local control till 28 weeks.

strong recommendation, high quality level of evidence (randomised trial) [8-13]

Local control for metastatic disease

We recommend wide surgical excision and adjuvant chemotherapy. Radiotherapy is recommended if positive surgical margins.

strong recommendation, high quality level of evidence (retrospective analysis of clinical trial, retrospective analysis of clinical trial) [19][20]

Definitive radiotherapy and adjuvant chemotherapy are recommended for irresectable tumours.

strong recommendation, high quality level of evidence (retrospective analysis of clinical trial, retrospective analysis of clinical trial) [19][20]

Management of metastases

For lung only metastases with partial response to neoadjuvant treatment, resection and whole lung irradiation are recommended.

Strong recommendation, high quality level of evidence (retrospective analysis, Prospective multicentre trial) [21][22]

For lung only metastases with complete response to neoadjuvant treatment, whole lung irradiation is recommended.

Strong recommendation, high quality level of evidence (retrospective analysis, Prospective multicentre trial) [21][22]

For bone metastases it is recommended to give radiotherapy to metastatic sites.

(retrospective analysis) [23]

4- Radiotherapy

Timing of RT

For patients receiving radiation therapy only it is recommended to be delivered at the beginning of week 13 concurrently with chemotherapy.

strong recommendation, high quality level of evidence (systematic review, Prospective trial) [24][25]

If post-operative radiotherapy is recommended, consider starting at week 15 concurrently with chemotherapy starting on day 1 of the cycle as soon as possible after surgery.

strong recommendation, high quality level of evidence (systematic review, Prospective trial) [24][25]

Patients with recent cord compression are recommended to start emergency concurrent radiotherapy and chemotherapy starting from day 1 first cycle.

strong recommendation, high quality level of evidence (systematic review, Prospective trial) [24][25]

Concurrent chemotherapeutic agents

Ifosfamide, etoposide, cyclophosphamide and vincristine should be given with radiotherapy. It is recommended to withhold doxorubicin with radiotherapy and re-institute after completion of radiation.

strong recommendation, high quality level of evidence (Randomised trial, systematic review) [13][26]

5- Treatment of recurrent/relapsed Ewing Sarcoma

Chemotherapy

Recommended chemotherapy combination

- Irinotecan and temozolomide in 21-day interval cycles, Or
- Ifosfamide, carboplatin and etoposide (if > 6 months).

strong recommendation, high quality level of evidence (prospective clinical trials) [27-28]

Surgery

Surgical resection of both local and metastatic sites (especially pulmonary) if feasible is recommended.

strong recommendation, high quality level of evidence (prospective observational study, retrospective analysis) [29][30]

Radiotherapy

Radiation is recommended either definitive or postoperative.

strong recommendation, high quality level of evidence (meta-analysis) [30]

6- Surveillance – Follow up - for Ewing Sarcoma patients

X-ray of the primary site is recommended every 4 months for the first 2 years and as clinically warranted.

strong recommendation, high quality level of evidence (prospective observational study, retrospective analysis) [31]

CT chest every 4 months is the recommended chest imaging in the first 2 years. Chest X-ray is recommended for chest imaging in later years.

strong recommendation, high quality level of evidence (prospective observational study, retrospective analysis) [31]

It is recommended to increase intervals of imaging of primary site and chest after 24 months and annually after 5 years (indefinitely).

strong recommendation, high quality level of evidence (prospective observational study, retrospective analysis) [31]

Clinical indicators for monitoring:

- Contrast enhanced MRI of primary site.
- CT chest.
- Confirmed Pathology.
- 2 weeks interval between cycles.

- local control after 9 weeks of chemotherapy.
- Radiotherapy referral.

Research Gaps

Comparison of outcome in terms of recurrence and toxicity between local control modalities in Egyptian patients.

Update of this guideline

This guideline will be updated whenever there is new evidence.

References

1) Gomez-Brouchet, A., Mascard, E., Siegfried, A., de Pinieux, G., Gaspar, N., Bouvier, C., Aubert, S., Marec-Bérard, P., Piperno-Neumann, S., Marie, B., Larousserie, F., Galant, C., Fiorenza, F., Anract, P., Sales de Gauzy, J., & Gouin, F. (2019). Assessment of resection margins in bone sarcoma treated by Neoadjuvant Chemotherapy: Literature review and guidelines of the Bone Group (GROUPOS) of the French sarcoma group and Bone Tumor Study Group (GSF-geto/RESOS). *Orthopaedics & Traumatology: Surgery & Research*, *105*(4), 773–780.
2) Kissane JM, Askin FB, Foulkes M, et al. Ewing's sarcoma of bone: clinicopathologic aspects of 303 cases from the Intergroup Ewing's Sarcoma Study. Hum Pathol 1983; 14:773-779.
3) Spector, L. G., Hubbard, A. K., Diessner, B. J., Machiela, M. J., Webber, B. R., & Schiffman, J. D. (2021). Comparative international incidence of Ewing Sarcoma 1988 to 2012. *International Journal of Cancer*, *149*(5), 1054–1066.
4) Treglia G, Salsano M, Stefanelli A, et al. Diagnostic accuracy of (1)(8)F-FDG-PET and PET/CT in patients with Ewing sarcoma family tumours: a systematic review and a meta-analysis. Skeletal Radiol 2012; 41:249-256.
5) Siegel MJ, Acharyya S, Hoffer FA, et al. Whole-body MR imaging for staging of malignant tumors in pediatric patients: results of the American College of Radiology Imaging Network 6660 Trial. Radiology 2013; 266:599-609.
6) Boddu S, Walko CM, Bienasz S, et al. Clinical Utility of Genomic Profiling in the Treatment of Advanced Sarcomas: A Single-Center Experience. JCO Precision Oncology 2018:1-8.

7) Campbell KM, Shulman DS, Grier HE, DuBois SG. Role of bone marrow biopsy for staging new patients with Ewing sarcoma: A systematic review. Pediatr Blood Cancer 2021;68: e28807.
8) Nesbit ME, Gehan EA, Burgert EO, et al. Multimodal therapy for the management of primary, nonmetastatic Ewing's sarcoma of bone: a long- term follow-up of the First Intergroup study. J Clin Oncol 1990; 8:1664- 1674.
9) Burgert EO, Nesbit ME, Garnsey LA, et al. Multimodal therapy for the management of nonpelvic, localized Ewing's sarcoma of bone: intergroup study IESS-II. J Clin Oncol 1990; 8:1514-1524.
10) Kolb EA, Kushner BH, Gorlick R, et al. Long-term event-free survival after intensive chemotherapy for Ewing's family of tumors in children and young adults. J Clin Oncol 2003; 21:3423-3430.
11) Shamberger RC, LaQuaglia MP, Gebhardt MC, et al. Ewing sarcoma/primitive neuroectodermal tumor of the chest wall: impact of initial versus delayed resection on tumor margins, survival, and use of radiation therapy. Ann Surg 2003; 238:563-567; discussion 567-568.
12) Brennan B, Kirton L, Marec-Berard P, et al. Comparison of two chemotherapy regimens in Ewing sarcoma (ES): Overall and subgroup results of the Euro Ewing 2012 randomized trial (EE2012). Journal of Clinical Oncology 2020; 38:11500-11500.
13) Womer RB, West DC, Krailo MD, et al. Randomized Controlled Trial of Interval-Compressed Chemotherapy for the Treatment of Localized Ewing Sarcoma: A Report from the Children's Oncology Group. Journal of Clinical Oncology 2012; 30:4148-4154.
14) Yock TI, Krailo M, Fryer CJ, et al. Local control in pelvic Ewing sarcoma: analysis from INT-0091--a report from the Children's Oncology Group. J Clin Oncol 2006; 24:3838-3843.
15) Dunst J, Jurgens H, Sauer R, et al. Radiation therapy in Ewing's sarcoma: an update of the CESS 86 trial. Int J Radiat Oncol Biol Phys 1995; 32:919-930.
16) Schuck A, Ahrens S, von Schorlemer I, et al. Radiotherapy in Ewing tumors of the vertebrae: treatment results and local relapse analysis of the CESS 81/86 and EICESS 92 trials. Int J Radiat Oncol Biol Phys 2005; 63:1562-1567.
17) DuBois SG, Krailo MD, Gebhardt MC, et al. Comparative evaluation of local control strategies in localized Ewing sarcoma of bone: a report from the Children's Oncology Group. Cancer 2015; 121:467-475.
18) Indelicato DJ, Keole SR, Shahlaee AH, et al. Definitive radiotherapy for ewing tumors of extremities and pelvis: long-term disease control, limb function, and treatment toxicity. Int J Radiat Oncol Biol Phys 2008; 72:871-877.
19) Haeusler J, Ranft A, Boelling T, et al. The value of local treatment in patients with primary, disseminated, multifocal Ewing sarcoma (PDMES). Cancer 2010; 116:443-450.
20) Paulino AC, Mai WY, Teh BS. Radiotherapy in metastatic Ewing sarcoma. Am J Clin Oncol 2013; 36:283-286.
21) Baumann BC, Nagda SN, Kolker JD, et al. Efficacy and safety of stereotactic body radiation therapy for the treatment of pulmonary metastases from sarcoma: A potential alternative to resection. J Surg Oncol 2016; 114:65-69.
22) Bolling T, Schuck A, Paulussen M, et al. Whole lung irradiation in patients with exclusively pulmonary metastases of Ewing tumors. Toxicity analysis and treatment results of the EICESS-92 trial. Strahlenther Onkol 2008; 184:193-197.

23) Casey DL, Wexler LH, Meyers PA, et al. Radiation for bone metastases in Ewing sarcoma and rhabdomyosarcoma. Pediatr Blood Cancer 2015; 62:445-449.
24) Mirzaei, L., Kaal, S. E. J., Schreuder, H. W. B., & Bartels, R. H. M. A. (2015). The neurological compromised spine due to Ewing sarcoma. what first. *Neurosurgery*, *77*(5), 718–725.
25) Boussios, S., Hayward, C., Cooke, D., Zakynthnakis-Kyriakou, N., Tsiouris, A. K., Chatziantoniou, A. A., Kanellos, F. S., & Karathanasi, A. (2018). Spinal Ewing sarcoma debuting with cord compression: Have we discovered the thread of Ariadne? *Anticancer Research*, *38*(10), 5589–5597.
26) Dunst J, Schuck A. Role of radiotherapy in Ewing tumors. Pediatr Blood Cancer 2004; 42:465-470.
27) Raciborska A, Bilska K, Drabko K, et al. Vincristine, irinotecan, and temozolomide in patients with relapsed and refractory Ewing sarcoma. Pediatr Blood Cancer 2013; 60:1621-1625.
28) Van Winkle P, Angiolillo A, Krailo M, Cheung YK, Anderson B, Davenport V, Reaman G, Cairo MS. Ifosfamide, carboplatin, and etoposide (ICE) reinduction chemotherapy in a large cohort of children and adolescents with recurrent/refractory sarcoma: the Children's Cancer Group (CCG) experience. Pediatr Blood Cancer. 2005 Apr;44(4):338-47.
29) Xue R, Lewis VO, Moon BS, Lin PP. Local recurrence of Ewing sarcoma: Is wide excision an acceptable treatment? J Surg Oncol 2019; 120:746-752.
30) Robinson SI, Ahmed SK, Okuno SH, et al. Clinical outcomes of adult patients with relapsed Ewing sarcoma: a 30-year single-institution experience. Am J Clin Oncol 2014; 37:585-591.
31) Bacci G, Forni C, Longhi A, et al. Long-term outcome for patients with non-metastatic Ewing's sarcoma treated with adjuvant and neoadjuvant chemotherapies. 402 patients treated at Rizzoli between 1972 and 1992. Eur J Cancer 2004; 40:73-83.