EE2012 PROTOCOL RADIOTHERAPY GUIDELINES

Recommandations du groupe Tumeur osseuses de la SFCE et du GSF-GETO

Rédacteurs: groupe des radiothérapeutes de la SFCE

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TITRE

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RECOMMANDATIONS

All cases should have local therapy discussed within specialist multidisciplinary team (MDT) meetings. The MDT should include medical/paediatric oncologists, surgeons and radiation/clinical oncologists. All French patients will be discussed in the paediatric radiotherapy web-conferencing meeting. Early discussion is strongly encouraged, ideally with first discussions at diagnosis, to allow optimal planning of local therapy.

Surgery should be considered as local therapy whenever feasible, as there is evidence that it is superior to radiotherapy alone as definitive local therapy. Radiotherapy is used as definitive local therapy in inoperable tumours, or in combination with surgery either pre- or postoperatively. These guidelines include discussion of the use of post-operative radiotherapy after intra-lesional surgery with residual microscopic disease (R1 excision). However, it should be noted that if surgery is planned carefully within a multidisciplinary team (MDT), and is carried out by experienced surgeons, this should be an unusual occurrence. Debulking procedures leaving macroscopic residual disease (R2 excision) should not be performed, although this may have occurred if a patient has had surgery for an unsuspected diagnosis, e.g. debulking surgery for spinal cord compression caused by a spinal tumour.

1. INDICATIONS FOR RADIOTHERAPY

Radiotherapy may be given to the primary tumour preoperatively, postoperatively or as definitive local therapy:

1.1. Pre-operative radiotherapy

Indications for planned preoperative radiotherapy include expected marginal resections, or if radiotherapy is anticipated to be required for another indication and it is judged at MDT discussion for there to be a technical advantage to giving radiotherapy prior to surgery.

1.2. Postoperative radiotherapy

Postoperative radiotherapy is considered for *all* patients *except* for:

- those who have had a wide local excision, defined as negative resection margins of at least 1mm; and a good histological response (>90% necrosis) to pre-operative chemotherapy; and with removal of all tissues originally involved by the pre-chemotherapy tumour volume;
- *or* for those in whom the anticipated adverse side effects of radiotherapy are sufficiently high to outweigh the additional benefit of radiotherapy for local control (anticipated to be an improvement of approximately 10%) for an individual patient. Reasons for deciding against radiotherapy may include:
    - Concerns about impaired wound healing following surgery and radiotherapy
    - Concerns about morbidity of giving radiotherapy to young patients

- Concerns about the increased risk of infection of a metallic prosthesis following radiotherapy
- Concerns about the risk of a 2nd radiation-induced malignancy

Specific indications *for* post-operative radiotherapy include:
For positive surgical margins with microscopic residual disease (R1 excision; <1mm or tumour up to edge of resection specimen) if further surgery to achieve negative margins is not possible

- For positive surgical margins with macroscopic residual disease (R2 excision), if further surgery to achieve negative margins is not possible (this should be an unusual situation)
- For negative surgical margins if all tissues involved by the original pre-chemotherapy tumour volume have not been excised
- For negative surgical margins if poor histological response (≤ 90% necrosis) to pre-operative chemotherapy
- Displaced pathological fracture of bone at primary site (unless it is possible to excise all contaminated tissue)
- For certain tumour sites, where local control is judged to be more difficult to achieve:
  - Spine and paraspinal sites - because in these sites excision is rarely complete, and is often intra-lesional
  - Pelvis and sacrum – because in these sites it is frequently difficult or impossible to be sure that the entire pre-chemotherapy tumour volume has been excised
  - Rib tumours when presenting with a pleural effusion

1.3. Definitive radiotherapy

Definitive radiotherapy is advised only in inoperable lesions. Inoperability is decided following MDT discussion, for tumours that cannot be resected completely, and in tumour sites where complete surgery would result in unacceptable morbidity or would be associated with a high risk of significant complications.

1.4. Whole lung radiotherapy

Whole lung radiotherapy is indicated in patients with pulmonary or pleural metastatic disease (R2pulm group) in both arms A and B.

2. TIMING OF RADIOTHERAPY

2.1. Radiotherapy to primary tumour

Surgery is scheduled to occur after 6 cycles of VIDE chemotherapy for arm A (i.e. week 18) or 9 cycles of VDC/IE for arm B (i.e. week 18). Radiotherapy can be given either prior to or after surgery, or as definitive local therapy, at this time. Early MDT discussions regarding local therapy, ideally after the first response evaluation, are strongly encouraged.

Patients who are to receive postoperative radiotherapy following surgery should continue with chemotherapy to allow recovery from surgery, wound healing and planning of radiotherapy.

Radiotherapy should be aimed to start during the 2nd to 4th cycles of post-operative consolidation chemotherapy. Delays in starting RT should be avoided. Actinomycin D (arm A) or doxorubicin (arm B) should to be omitted during radiotherapy, and re-introduced after completion of radiotherapy after acute reactions have resolved (see section 7). For patients who have had a biological reconstruction as part of their surgery, it may be desirable to delay post-operative radiotherapy in order to allow time for the bone graft to unite.

2.2. Whole lung radiotherapy

For R2pulm patients, whole lung radiotherapy is given on completion of consolidation chemotherapy.

3. RADIOTHERAPY TECHNIQUES AND DELIVERY

Patients will be treated with CT-planned conformal 3D radiotherapy using dose volume histograms to assess doses to organs at risk. Intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), or tomotherapy can be used at centres with access to this technique, and should be particularly considered for head and neck, pelvic and paraspinal tumours in order to achieve optimal dose distributions and dose delivery. Proton beam radiotherapy is also permitted as long as this does not compromise delivery of chemotherapy. Patients should be immobilised using customised immobilisation devices for limb, and head and neck, tumours. Image guided radiotherapy (IGRT) should be used, according to institutional protocols. Dose specification is according to the ICRU 50 and 62 reports.

4. TARGET VOLUME DEFINITION

Target volumes are defined in accordance with ICRU 50 and 62. The principle of treatment is to treat tissues originally involved by tumour at initial diagnosis prior to chemotherapy. A shrinking volume technique may be used in some situations following surgery, with a phase I to include the tumour and involved tissues, and scars and prosthesis; and a smaller phase II to include the tumour and involved tissues only.

N.B. Please also see site-specific guidelines in section 6.

4.1. Pre-operative and definitive radiotherapy

4.1.1.Gross tumour volume (GTV)

GTV is defined as the visible tumour on imaging at its maximal extent (using CT, PET, bone and MRI scans, as available) prior to any chemotherapy or surgery. MRI is usually the minimal optimal imaging modality. For patients who have tumours with ‘pushing’ margins extending into body cavities (e.g. abdomen, thorax), GTV will required modification, because with regression of the tumour, normal tissues such as bowel and lung will have returned to their normal position.

4.1.2.CTV

CTV should encompass any sites of potential microscopic extension of GTV, and should be at least GTV + 1.5 – 2cm (depending on exact anatomical location). It should also take into account

anatomical barriers to tumour spread such as fascial boundaries and bone.

4.1.3.PTV

PTV is defined from CTV, with a margin to account for day-to-day set-up variation, and if relevant, internal organ motion. This will vary according to tumour location in the body, and is specific to individual institutions. PTV will be typically 0.5 – 1.0cm.

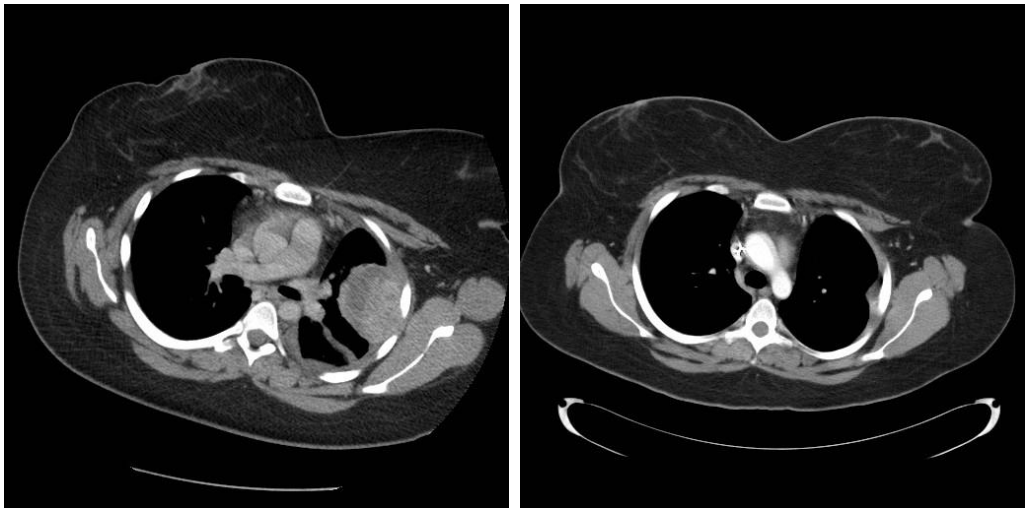
4.2. Post-operative radiotherapy

4.2.1.GTV

For patients who have undergone surgery, there is by definition no GTV, but consideration should be given to reconstructing the pre-treatment GTV to aid decisions made in the voluming of CTV.

GTV is defined as the visible tumour on imaging at its maximal extent (using CT, PET, bone and MRI scans, as available) prior to any chemotherapy or surgery. MRI is usually the minimal optimal imaging modality. For patients who have tumours with 'pushing' margins extending into body cavities (e.g. abdomen, thorax), GTV will required modification, because with regression of the tumour, normal tissues such as bowel and lung will have returned to their normal position.

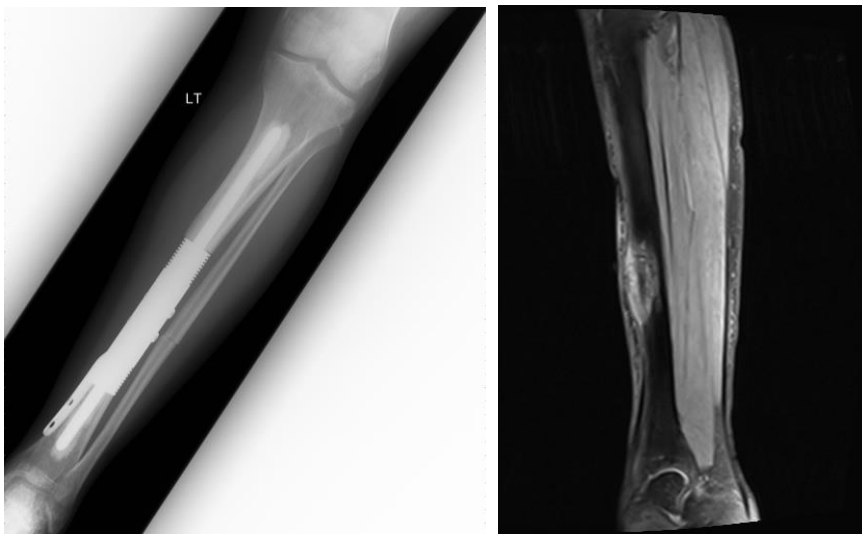
Figure 1: Ewing's sarcoma of rib, demonstrating returning of lung to normal position following regression of tumour on induction chemotherapy.



4.2.2.Clinical target volume 1 (CTV1)

CTV1 should encompass any sites of potential microscopic extension of GTV, or of contamination by GTV, including metallic prostheses, drain sites and surgical scars (if feasible), and should be at least GTV + 1.5 – 2cm radially (depending on exact anatomical location). It should also take into account anatomical barriers to tumour spread such as fascial boundaries and bone. It may not be necessary to treat the entire prosthesis, depending on its structure and size; this should be decided on an individual patient basis, balancing the need to include the prosthesis, and the resulting additional normal tissue that must be treated to achieve this. Similarly, it may not be necessary or possible to treat the entire scar, particularly if its inclusion results in a significant increase in treatment volumes with a resultant anticipated increase in the morbidity of radiotherapy.

Figure 2: Ewing's sarcoma of tibial shaft, with large prosthesis that would not need to be completely included in CTV.



4.2.3.Clinical target volume 2 (CTV2)

As with CTV1, CTV2 should encompass any sites of potential microscopic extension of tumour (GTV), and should be no less that GTV + 1 – 2cm (depending on exact anatomical location). However, CTV2 does not need to include scars and drain sites. It should take into account anatomical barriers to tumour spread such as fascial boundaries and bone.

4.2.4.Planning target volume 1 and 2 (PTV1/2)

PTV1 and 2 are defined from CTV 1 and 2 respectively, with a margin to account for day-to-day set-up variation, and if relevant, internal organ motion. This will vary according to tumour location in the body, and is specific to individual institutions. PTV1 and 2 will be typically 0.5 – 1.0cm.

4.3. Whole lung radiotherapy

The CTV is the entire pleural cavity/surface of both lungs. A margin, usually at least 1cm is added for PTV. Volumes can be drawn, or alternatively treatment fields can be placed by simulation or virtual simulation. Respiratory-gated radiotherapy can be used if desired.

5. RADIOTHERAPY DOSE AND FRACTIONATION

5.1. Pre-operative radiotherapy

The total dose for preoperative irradiation is 50.4 Gy in 28 fractions in a single phase to the PTV. If there are concerns about organ tolerance or wound healing, then this dose can be reduced to 45 Gy in 25 Gy fractions.

5.2. Post-operative radiotherapy

The total dose for postoperative radiotherapy is 54 Gy in 30 fractions, delivered as 45 Gy in 25 fractions to PTV1, and 9 Gy in 5 fractions to PTV2.

5.3. Definitive radiotherapy

The total dose for definitive radiotherapy is 54.0 Gy in 1.8 Gy fractions, delivered as a single phase. A boost of 5.4Gy in 3 fractions may be considered if desired, keeping within standard normal tissue dose constraints.

5.4. Whole lung radiotherapy

The dose for whole lung radiotherapy is 15 Gy in 10 fractions for patients <14 years, or 18 Gy in 12 fractions for patients ≥14 years. Dose may be specified to 100% for an optimised plan, or to the mid plane dose (MPD) for simulated opposed fields. However, it should be noted that this will result in a dose of approximately 10% higher in the lungs than that prescribed, and so optimisation of dosimetry is recommended if fields are simulated.

5.5. Fractionation

Conventionally fractionated radiotherapy (once daily fractions, five 1.8 Gy fractions per week) is the preferred fractionation schedule. In very young children, fractionation using 1.6Gy fractions may be considered.

6. CONSIDERATIONS FOR SPECIFIC TUMOUR LOCATIONS

6.1. Extremity tumours

The limb should be immobilised with a customised immobilisation device. Care should be taken to include any adjacent skip metastases. The CTV along the length of the bone should be 1 – 2 cm beyond GTV in the bone, and 2 cm beyond the pre-chemotherapy extra-osseous mass. Joints and epiphyseal plates should be spared if possible, as long as this does not compromise PTV coverage. An un-irradiated strip of normal tissue ('corridor') along the length of the limb should be spared in order to maintain lymphatic drainage and to reduce the risk of lymphoedema. There are no data to allow definition of the width or volume to be spared as the corridor, but it is suggested that it should be approximately 0.25 of the circumference, which equates to approximately 10% of the cross-sectional area of the limb. For IMRT, VMAT or tomotherapy plans, attention should be paid to limiting the dose to areas outside PTV1, and to limiting a corridor as described above to no more than 35 Gy.

6.2. Tumours of the head and neck and skull

Patients with head and neck/skull tumours should be immobilised with a customised immobilisation device. The margins added to GTV for CTV may be smaller than 1.5 – 2cm, as such margins are unlikely to be achievable because of local critical structures (e.g. eye, optic chiasm). CTV to PTV margins are also expected to be smaller due to the better immobilisation possible at these locations. Head and neck/skull tumours are likely to benefit from an IMRT/VMAT plan.

6.3. Pelvic/sacral tumours

Pelvic and sacral tumours will frequently present with large pre-chemotherapy tumour volumes that extend into the pelvic and abdominal cavities. These tumours can regress significantly, with normal tissues such as bowel returning to their normal locations. Voluming of GTV and CTV will need to take this into account so that large volumes of normal tissues are not treated un-necessarily. Surgical placement of spacer devices may be helpful, in order to displace bowel away from the involved bone. Pelvic and sacral tumours may benefit from an IMRT/VMAT plan.

6.4. Chest wall/rib tumours

These tumours may also present with large pre-chemotherapy tumour volumes that extend into the thoracic cavity, displacing lung and pleura. Regression of the tumour during induction chemotherapy often result in lung returning to its normal location, and voluming of GTV and CTV will need to take this into account to avoid unnecessary treatment of large volumes of lung. If pleural involvement was observed at presentation with a pleural effusion (even if cytology was negative), then the whole pleural cavity of the hemithorax will need to be included, treated as for the guidelines for whole lung radiotherapy. Hemithorax radiotherapy is then followed by treatment of GTV to a total dose of 54 Gy if radiotherapy to the primary site is indicated.

6.5. Spinal/paraspinal tumours

GTV should be treated with an appropriate margin around any soft tissue extension, and should receive a maximum dose of no more than 50.4 Gy in 28 fractions. CTV should normally include one unaffected vertebra above and below the affected vertebra, and should also include the scar and any metallic stabilisation rods and cages if the patient has had surgery (as long inclusion of these does not increase the CTV to an unreasonably large size); a smaller CTV2 can be used if appropriate, that does not completely encompass scars, and rods and cages. PTV1 should be treated to a dose of 45 Gy in 25 fractions, and PTV2 to a dose of 5.4 Gy in 3 fractions. Otherwise, PTV is treated in a single phase to a total dose of 50.4 Gy in 28 fractions.

Spinal and paraspinal tumours may benefit from an IMRT/VMAT/tomotherapy plan, in order to achieve optimal doses to PTV while keeping the spinal cord dose within tolerance. However, the presence of metal rods and cages may produce dosimetric uncertainties when using IMRT/VMAT/tomotherapy techniques, which should therefore be used with caution.

7. CHEMOTHERAPY DURING RADIOTHERAPY

7.1. Actinomycin D

Actinomycin D given during VAC and VAI consolidation chemotherapy (arm A) should be omitted during central axial irradiation, or where there are concerns for acute toxicity that may be exacerbated by actinomycin D. It can be re-introduced again on completion of radiotherapy. Radiotherapy should start no sooner than 1 week after the last dose of actinomycin, and actinomycin should be re-introduced no sooner than 1 week after completion of radiotherapy.

7.2. Doxorubicin

Doxorubicin given during VDC chemotherapy (arm B) should be omitted during radiotherapy, and can be reintroduced on completion of radiotherapy. Radiotherapy should start no sooner than 1

week after the last dose of doxorubicin, and doxorubicin should be re-introduced no sooner than 1 week after completion of radiotherapy. Longer delays (up to 3 weeks) should be used if bowel or heart are within the radiotherapy fields.

8. DOSE LIMITS TO NORMAL TISSUES

Clinicians are referred to the recent QANTEC publication for limits to normal tissues (1).

REFERENCES

1. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S10-9. Epub 2010/03/05.