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Critical Review

Radiation Therapy for Solitary Plasmacytoma and Multiple Myeloma: Guidelines From the International Lymphoma Radiation Oncology Group

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Purpose: To develop guidelines for the work-up and radiation therapy (RT) management of patients with plasma cell neoplasms.

Methods and Materials: A literature review was conducted covering staging, work-up, and RT management of plasma cell neoplasms. Guidelines were developed through consensus by an international panel of radiation oncologists with expertise in these diseases, from the International Lymphoma Radiation Oncology Group. RT volume definitions are based on the International Commission on Radiation Units and Measurements.

Results: Plasma cell neoplasms account for approximately one-fifth of mature B-cell neoplasms in the United States. The majority (~95%) are diagnosed as multiple myeloma, in which there has been tremendous progress in systemic

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therapy approaches with novel drugs over the last 2 decades, resulting in improvements in disease control and survival. In contrast, a small proportion of patients with plasma cell neoplasms present with a localized plasmacytoma in the bone, or in extramedullary (extraosseous) soft tissues, and definitive RT is the standard treatment. RT provides long-term local control in the solitary bone plasmacytomas and is potentially curative in the extramedullary cases. This guideline reviews the diagnostic work-up, principles, and indications for RT, target volume definition, treatment planning, and follow-up procedures for solitary plasmacytoma. Specifically, detailed recommendations for RT volumes and dose/fractionation are provided, illustrated with specific case scenarios. The role of palliative RT in multiple myeloma is also discussed.
Conclusions: The International Lymphoma Radiation Oncology Group presents a standardized approach to the use and implementation of definitive RT in solitary plasmacytomas. The modern principles outlining the supportive role of palliative RT in multiple myeloma in an era of novel systemic therapies are also discussed.

Introduction

Plasma cell neoplasms are mature B-cell malignancies consisting of clonal plasma cells that are terminally differentiated B cells characterized by immunoglobulin secretion. There is a wide spectrum of clinical features, from monoclonal gammopathy of unknown significance to symptomatic myeloma to plasma cell leukemia. The majority of plasma cell tumors are diagnosed as multiple myeloma (MM) and tend to affect older adults. Although the mainstay treatment for MM is systemic chemotherapy, radiation therapy (RT) often has an important supportive role, offering very effective symptom relief for tumor deposits (plasmacytomas) in bone or soft tissue. As effective systemic therapies have evolved over the last decade, leading to longer patient survival but with episodic disease activity or slow progression, the role of RT for durable local control of symptomatic tumors is even more important. A small proportion of plasma cell neoplasms (approximately 5% to 6%) will manifest as a solitary plasmacytoma, either in bone or in extramedullary tissues. These are of particular interest to radiation oncologists as the standard management with curative intent has been definitive RT. Plasma cell neoplasms are radiation-sensitive tumors. However, with the advent of modern imaging and RT techniques and the use of multiple new systemic treatment approaches, there is a lack of updated guidelines for the integration of RT. The present guidelines cover optimal imaging assessment, clinical target volume (CTV) definition, the need for prophylactic coverage of regional nodes, and the coverage of surgical hardware in the postoperative setting. The International Lymphoma Radiation Oncology Group (ILROG) assembled an expert panel to review the literature and generate consensus guidelines regarding the planning of RT in these diseases.

Solitary Plasmacytoma

Definition

Solitary plasmacytoma (SP) is a plasma cell disorder characterized by localized accumulation of neoplastic monoclonal plasma cells in bone, or in soft tissues (with no skeletal component), without any evidence of systemic involvement as demonstrated by the lack of clonal plasma cells in the bone marrow and absence of features of end-organ damage (Table 1) (1). When all criteria are satisfied except for the presence of a small clone of plasma cells in the bone marrow, quantified at $<10\%$ involvement, the condition can be defined as "solitary plasmacytoma with minimal marrow involvement" (1). This definition is useful prognostically as subclinical bone marrow involvement detected by sensitive tests such as flow cytometry predicts a high rate of progression to MM (56% to 70%) over a short period of time (2 to 3 years) (1, 3, 4).

Based on their location, SPs have been classified into 2 groups, the first being solitary bone plasmacytoma (SBP), which frequently occurs in the axial skeleton. SBP has a high risk of progression to MM, leading some clinicians to regard it as an early stage of MM. The second group is solitary extramedullary plasmacytoma (SEP), a less common diagnosis (20% to 30% of cases) (5, 6), occurring mostly in the head and neck region (eg, nasal cavity, paranasal sinuses, and nasopharynx) but also seen rarely arising in soft tissues, gastrointestinal tract, skin, and lymph nodes (5, 6). In contrast to SBPs, SEPs are often localized tumors, and local therapy achieves long-term control with a higher reported cure rate than that for SBP (5, 6).

Rarely a SP may be associated with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin abnormalities), with the diagnosis confirmed by the presence of both the mandatory major criteria (polyneuropathy and monoclonal plasma cell proliferative disorder), 1 of the 3 other major criteria (Castleman's disease, sclerotic bone lesions, and elevated vascular endothelial growth factor level) and 1 of the 6 minor criteria (organomegaly, endocrinopathy [other than diabetes or hypothyroidism], skin changes, extravascular volume overload, papilledema, and thrombocytosis) (2). Definitive RT can result in long-term local control of the plasmacytoma, with improvement or amelioration of the symptoms of POEMS syndrome in up to half of the patients (7).

Evaluation for solitary plasmacytomas

Mandatory laboratory investigations for any suspected case of plasma cell neoplasm include complete blood count with

Table 1 Diagnostic criteria for solitary plasmacytoma, as recommended by the International Myeloma Working Group (1). The diagnosis of solitary plasmacytomas is based on the exclusion of systemic plasma cell disorders.

Plasma cell disorder	Diagnostic criteria
Solitary bone plasmacytoma, or solitary extramedullary plasmacytoma	• Biopsy-proven solitary destructive lesion of bone or soft tissue mass of clonal plasma cells. • Absence of clonal plasma cells in bone marrow biopsy and aspirate. • Normal skeletal survey and magnetic resonance imaging (or computed tomography) of spine and pelvis (except for the primary solitary lesion) • If available positron emission tomography/computed tomography showing solitary lesion (2) • Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) attributed to a plasma cell proliferative disorder
Solitary plasmacytoma with minimal marrow involvement	• As above but: • Clonal bone marrow plasma cells are detected but quantified to be $<10\%$

peripheral blood and smear review, biochemistry screen with serum calcium, electrolytes, lactate dehydrogenase, β2-microglobulin, and creatinine. Electrophoresis of serum and urine (24-hour urine), followed by immunofixation to confirm and type of M-protein present should be performed. Nephelometric quantification of total immunoglobulin isotype and serum light chain levels should be a part of the work-up. Bone marrow aspirate and trephine biopsy are mandatory to confirm the absence of clonal plasma cells (for SP) or the presence of $<10\%$ clonal plasma cells (SP with minimal bone marrow involvement).

Imaging tests include assessment of the extent and severity of the plasmacytoma at presentation. In spite of evolution in imaging technology, skeletal survey still remains the standard imaging modality for screening at diagnosis. It has advantages of low cost and universal availability. However, conventional radiography has many limitations, including low sensitivity, because lesions are detected only if greater than 30% of the bone trabeculae is destroyed, which leads to at least 20% false-negative results (8, 9). In addition, conventional imaging can neither detect nor quantify diffuse bone marrow infiltration or extraosseous lesions. Cross-sectional imaging methods with computed tomography (CT) and magnetic resonance imaging (MRI) should be used to complement radiographic imaging in diagnosis, staging, and defining the local extent of the plasmacytoma. A practical advantage of a CT scan is that it can be used for a guided needle biopsy of a deep-seated lesion for histologic confirmation. CT also forms the basis for RT planning, or surgical intervention if required. In general, CT scans cannot detect diffuse bone marrow infiltration, and small extraosseous lesions may be missed.

MRI allows better visualization of the medullary cavity and is therefore very useful for SP involving a long bone. It is indispensable for head and neck presentations and lesions infiltrating the spine, epidural space, or soft tissues and for evaluations of nerve root or spinal cord compression. On MRI, plasmacytomas are typically hypointense on T1-weighted images and enhance with contrast. They are hyperintense on T2-weighted and short tau inversion recovery (STIR) sequences (Fig. 1). Owing to its ability to visualize large volumes of bone marrow without radiation exposure, MRI of the entire spine, including the sacrum and sacroiliac areas, has also become a favored method for evaluating disease within the bone marrow as a screening test (Fig. 1). Therefore MRI should be a routine staging procedure in the work-up of SP. This is consistent with the recommendations of the International Myeloma Working Group (10, 11).

Clinical experience with 18-fluoro-deoxyglucose positron emission tomography (^{18}FDG-PET/CT) imaging in patients with plasma cell neoplasms has been in rapid evolution. The updated 2017 International Myeloma Working Group guidelines consider PET/CT as a valuable tool in many indications, including the work-up of patients with MM, and in fact stated that PET/CT is mandatory to confirm a diagnosis of solitary plasmacytoma (12). Studies have shown PET/CT to be highly sensitive for detecting myeloma deposits (12-15). It can reveal additional lesions in almost 30% of the patients diagnosed with SP by MRI (16, 17). PET/CT and MRI are complementary for identifying diffuse spinal disease or excluding false positives for either modality done alone. Therefore, PET/CT could be useful in SP as a screening tool for myeloma lesions (12), as it examines the whole body in a single study, and would be particularly helpful in further clarification of ambiguous CT and/or MRI findings. PET/CT has also been found to demonstrate faster normalization as an imaging finding (FDG uptake) than does MR imaging following therapy (18). ILROG recommends that PET/CT should be performed as standard work-up for SP (Figs. 2-5), particularly when whole body MRI is of limited availability (12). The limitations of PET include its inability to detect very small lytic skeletal lesions, particularly if located in the skull, and lower sensitivity than MRI in the detection of early diffuse patterns of bone marrow involvement (13). In addition,

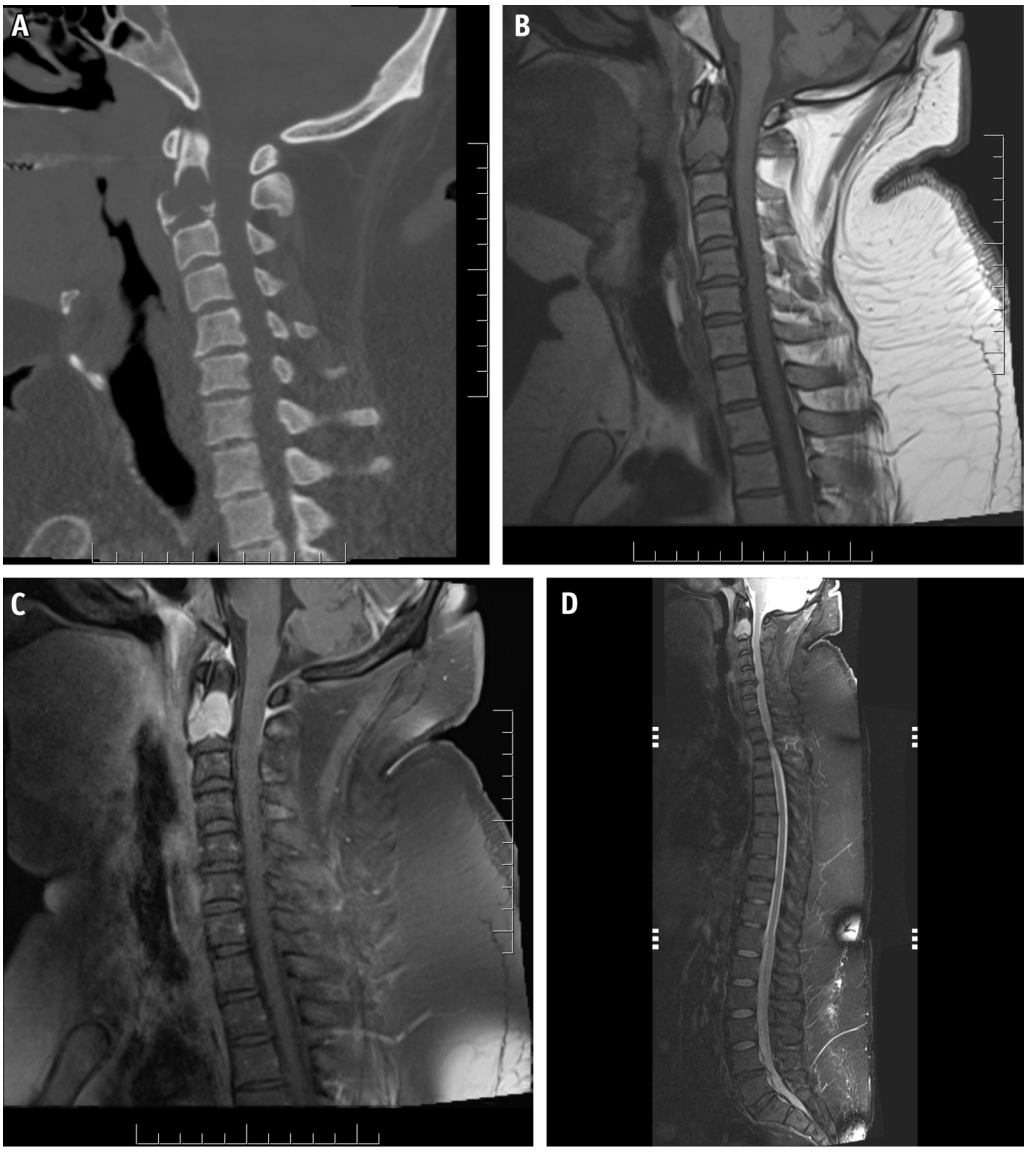

Fig. 1. Solitary bone plasmacytoma of C2 vertebra in a 46-year-old man, sagittal computed tomography scan, bone window (A). Magnetic resonance T1-weighted image showing the tumor to be isointense compared with normal vertebra (B), but enhanced with contrast (C). Screening magnetic resonance image for the whole spine on STIR sequence typically demonstrates high signal intensity of the plasmacytoma at C2 compared with the normal vertebrae of the rest of the spine (D).

occasionally poor spatial resolution/registration with CT scanning is observed. It is recognized that with the routine use of increasingly sensitive imaging procedures (MRI, PET/CT), subclinical lesions, when detected, will upstage patients, resulting in treatment decision dilemmas of whether to treat with systemic chemotherapy as for symptomatic myeloma, definitive RT alone, or some combination of the two. This topic is discussed in the next section.

Management of SP

SBPs have a high risk of progression to MM (65% to 84% in 10 years and close to 100% by 15 years) (6, 19-23). In contrast, SEPs have a lower risk (10% to 30% over 10 years) of progression to MM (6, 23-26) but have a slightly higher risk of local recurrence (24). Therefore, the optimal therapeutic strategy for SPs should aim to achieve durable long-term local control with minimal morbidity, provide effective pain control, and in certain instances stabilize weight-bearing bones (eg, spine). Currently, the standard of care for SBP and SEP is definitive local RT, as it provides excellent local control (85% to 90%) that may translate into a durable remission and even cure (27).

Certain special situations warrant surgical intervention. For instance, pathologic fracture or surgical instability of a weight-bearing long bone (eg, femur) will require consultation with an orthopedic surgeon for consideration of surgical stabilization. Similarly, decompressive surgery is indicated in the case of neurologic compromise due to spinal cord compression. Surgical intervention with stabilization

procedure of the spine is also indicated in patients who develop pain due to structural compromise within the vertebrae (eg, compression fracture with or without a bone fragment displaced into the spinal canal) or vertebral instability, or a combination of the above situations (28). Typically surgery is pursued prior to RT but usually does not negate the need to proceed with definitive RT in the postoperative period, usually 4 to 6 weeks after surgery to allow adequate healing. In general, a definitive surgical excision alone can be considered as acceptable treatment only for small tumors in anatomic locations where clear margins are attained with minimal morbidity. Examples might include a cutaneous lesion or a solitary lung lesion where a lobectomy has been performed. In the situation of incomplete surgical removal or positive surgical margins, definitive RT should be strongly considered to achieve optimal local control, as surgery alone without RT is associated with an unacceptably high local recurrence risk (6, 24).

Vertebroplasty is a commonly performed procedure in cases of structural instability due to MM (29, 30) but has not yet been reported to be useful as a primary treatment for SBP. This procedure if used alone is likely to be of limited value initially for vertebral disease with epidural extension and/or spinal cord compression as there is a small risk of further displacing the tumor into the spinal canal, causing neurologic deterioration (31, 32). When patients are properly selected, the risks of tumor extravasation into the spinal canal or cement leakage into the epidural space following vertebroplasty are rare complications, limited to case reports (30-33). Performing vertebroplasty after RT is a good strategy to reduce these risks since RT would reduce the tumor bulk and potentially induce remineralization. Vertebroplasty can be very useful to alleviate pain associated with a persistently collapsed vertebra, similar to the approach in patients with MM (30).

The use of sensitive tests to detect small tumor burden in the body is routine in many specialized centers during the work-up of a patient with SP. These may include flow cytometry of the bone marrow, cytogenetics, and imaging such as MRI and PET/CT. The identification of 2 or more separate plasmacytoma lesions, in the setting of a negative bone marrow result (plasma cell quantification of $<10\%$), is defined as MM (1). Despite a negative bone marrow test result by morphology ($<10\%$ plasma cells) and an absence of abnormal calcium level, renal impairment, anemia, and bone lesions (CRAB features), the presence of a small burden of disease away from the SP location suggests a high risk of progressing to symptomatic MM over a short period of time (2-3 years) (3, 4, 11, 22, 34). Of interest, one of the larger published series of SBP with patients treated prior to 2001 ($n = 206$) indicated that the progression rate to MM following RT is more rapid in the first 3 years ($\sim$14% per year) than in the subsequent 7 years ($\sim$3% to 4% per year), reaching a 10-year rate of 65% (6). This suggests that subclinical disease most likely existed in up to 40% of these patients with SBP at the time of definitive RT, and the earlier detection of this subclinical disease could identify patients amenable to alternate treatment approaches such as systemic therapy with novel agents, with or without RT depending on the clinical situation. Yet some argue that MM with minimal disease burden and absence of symptoms remains incurable; therefore the SP should still be treated with definitive RT with deferred systemic therapy until symptomatic progression to MM (28). In practice, the decision to give systemic therapy is made by the attending hematologist or medical oncologist and should be individualized based on considering other important factors such as age, performance status, size and location of the SP (hence the desirability of attaining local control with definitive RT), the number and pattern of focal bone lesions detected, monoclonal protein level, and molecular or cytogenetic characterization (if available), which may indicate biologically aggressive disease. In the situation of equivocal imaging, or when a false-positive finding is suspected, a biopsy is recommended if the result is going to influence the treatment decision. Of note, there is no high-level evidence showing a benefit of combined modality therapy over RT alone for patients with SP. One small, outdated randomized study ($n = 53$) of RT and 3 years of adjuvant melphalan suggested a lower progression rate from SBP to MM (12%, vs 54% with RT alone, $P < .01$, median follow-up 8.9 years) (35). A small phase 2 study ($n = 5$) using novel agents (lenalidomide or bortezomib) combined with RT (40 Gy) suggested that this is a safe and feasible combination and is worthy of further study (36).

Definitive RT for SP

SPs are radioresponsive tumors with RT alone achieving excellent long-term local control (79% to 91%) (6, 20, 21, 23, 37-39). For SBP, the local tumor and the surrounding extension of microscopic disease require defintive RT treatment (Fig. 3). Dose and planning guidelines are discussed later. The clinical management and RT parameters may sometimes be modified by an estimation of the rate of progression to MM, given that it is known that the majority of these patients will subsequently experience systemic disease progression and will most likely require some form of systemic therapy in the future. For SEP, definitive RT is used as a curative therapeutic strategy. A particularly common scenario is SEP arising in the head and neck region (Figs. 2 and 4). Approximately 25% of SEP in the head and neck area will be found to have regional nodal disease on imaging incorporating MRI and PET/CT (39). Involved nodal tissue requires definitive RT coverage and consideration of elective coverage of adjacent nodes deemed to be at risk. However, in the absence of nodal involvement on modern imaging, there is controversy regarding the benefit of prophylactic nodal irradiation, particularly if the SEP is involving Waldeyer's ring structures, such as the nasopharynx (Fig. 2). Before the advent of conformal RT techniques and modern imaging, it was common practice to cover cervical lymph nodes prophylactically, and regional nodal failures were rarely seen (20, 26). Several retrospective studies were able to analyze

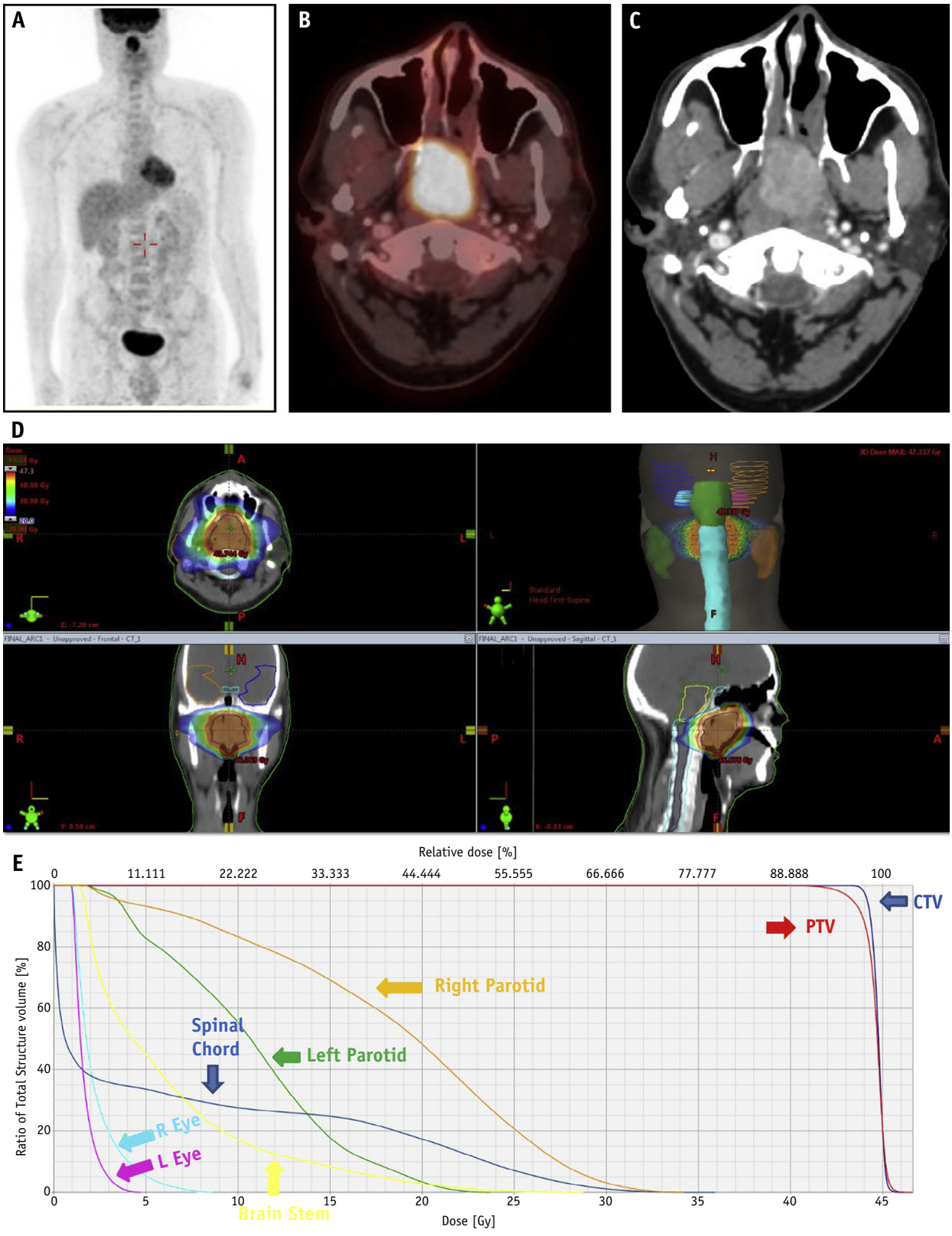

Fig. 2. Solitary extramedullary plasmacytoma of nasopharynx, fluoro-deoxyglucose avid on maximum intensity projection positron emission tomography scan image (A), and on axial image (B), with corresponding axial computed tomography scan image showing contrast enhancement of the plasmacytoma (C). Definitive radiation therapy with volumetric arc therapy, with a clinical target volume covering the entire nasopharynx, without intentional coverage of regional lymph nodes. Total dose 45 Gy in 25 fractions, dose distribution (20 Gy dose wash in blue) illustrating sparing of parotid gland, with mean dose

the subgroup of patients when elective nodal radiation was not practiced and came to the conclusion that nodal recurrence rates remained very low (~5%) (20, 40, 41). With the advent of sophisticated imaging (MRI and PET/CT), the ILROG panel consensus is that elective lymph node coverage is not required for SEP (Figs. 2 and 4) unless there is persuasive clinical evidence to indicate a high risk of nodal involvement, such as very bulky primary disease or proximity to the primary lesion when nodal coverage will not increase the treatment toxicity in a significant way.

RT Dose Consideration for SP

The optimal dose of radiation for SP is not well established, since data on dose-response relationships are weak in most of the studies owing to the relatively small number of patients and narrow range of doses used in an uncontrolled fashion. A large multi-institutional study (n = 258) did not show a dose-response relationship beyond 30 to 35 Gy (6). Despite this, it is common practice to use a dose of 40 to 45 Gy (28). In a retrospective review of 81 patients, Mendenhall et al reported a local control rate of 94% with 40 Gy or above, compared with 69% for doses lower than 40 Gy (42). Several studies have reported using larger RT doses (range 45 to 60 Gy) without any evidence of advantage from the higher doses; sporadic local failures have been reported even with doses of 50 to 60 Gy (22, 37). A small retrospective study from Princess Margaret Hospital reported the lack of dose-response relationship above 35 Gy (21) for small tumors <5 cm (100% local control for SBP <5 cm in maximum diameter). The authors suggested that higher RT doses may be required only for bulkier tumors measuring 5 cm or more in maximum diameter. There is also some evidence that SEP is optimally controlled with a dose of 40 Gy or more (25, 39, 43). Owing to a lack of phase 3 clinical trial data addressing the optimal RT dose, most clinicians follow the published guidelines, with the National Comprehensive Cancer Network recommending a minimum dose of 40 Gy regardless of tumor size (27), similar to the United Kingdom Myeloma Forum's guidelines (28). Based on the results from retrospective studies and the consensus opinion of the ILROG panel, the following dose guidelines are recommended (with 1.8-2 Gy daily fractions):

- SBPs <5 cm: total dose 35 to 40 Gy (Based on the earlier discussion, ILROG determines that for small SBPs it is acceptable to prescribe 35 Gy, which is different from the National Comprehensive Cancer Network's recommendation of minimum total dose of 40 Gy.)
- SBPs ≥5 cm: total dose 40 to 50 Gy
- SEPs: total dose 40 to 50 Gy (In cases of small, well-defined, or postexcision with positive margins, 40 Gy is acceptable.)

For patients with SP with minimal bone marrow involvement, or other imaging evidence of minimal involvement of the bony skeleton, the total dose and fractionation can be modified (eg, to a more hypofractionated regimen) as is clinically appropriate (see the section on RT volume and planning guidelines).

MM Palliation With RT

Osteolytic lesions are observed at diagnosis in almost 70% to 80% of patients with MM (44, 45). Bone involvement, often associated with tumor extension into surrounding soft tissues, commonly manifests as bone pain, pathologic fractures, and neurologic compromise such as spinal cord compression, nerve root compression, and cranial nerve deficits (46, 47). Patients with compression fractures or impending fractures of weight-bearing bones should be first considered for surgical stabilization prior to RT. For pain due to vertebral body collapse in the absence of spinal cord compression, when soft tissue disease is not apparent, vertebroplasty can be beneficial. A surgical evaluation is often recommended for cases of rapidly evolving symptomatic spinal cord compression, because a prompt intervention may improve the chance of immediate and sustained neurologic recovery (48, 49). RT alone has also been shown to be a very effective palliative treatment for patients with spinal cord compression. A recent study of 238 myeloma patients has shown excellent response rates (97%), local control (93% at 1 year and 82% at 2 years), and functional outcomes (64% of nonambulatory patients regained the ability to walk) in patients treated with RT alone (50). Moreover, RT has shown to provide pain relief with reduction of analgesic drugs, ameliorate neurologic symptoms, promote recalcification of bone, and improve both motor function and quality of life in patients with MM. The advent of novel agents has certainly improved the outcome of patients (51) and has raised the importance of choosing the most effective treatment for each patient, moving from a "population-based" therapeutic strategy to a "patient-tailored" approach. In this regard, Rades et al (52) have recently designed a prognostic score for elderly patients (>65 years) presenting with spinal cord compression from MM that allows for an accurate estimation of the survival prognosis. Combining 4 factors that were significantly associated with survival on univariate analysis (age, myeloma type, performance status, ambulatory status prior to RT), the authors identified 3 cohorts with different outcomes (OS at 1 year was 96%, 43%, and 0%, respectively, for the 3 groups). Further refinements in prognostic scores (eg, attempts to integrate biologic and molecular parameters) will be invaluable in guiding decision making (53, 54).

18.0 Gy (right) and 10.6 Gy (left) (D), and dose volume histogram (E). Mean parotid doses of 10 to 15 Gy is usually achievable in centrally located tumors using intensity-modulated radiation therapy or volumetric arc therapy techniques.

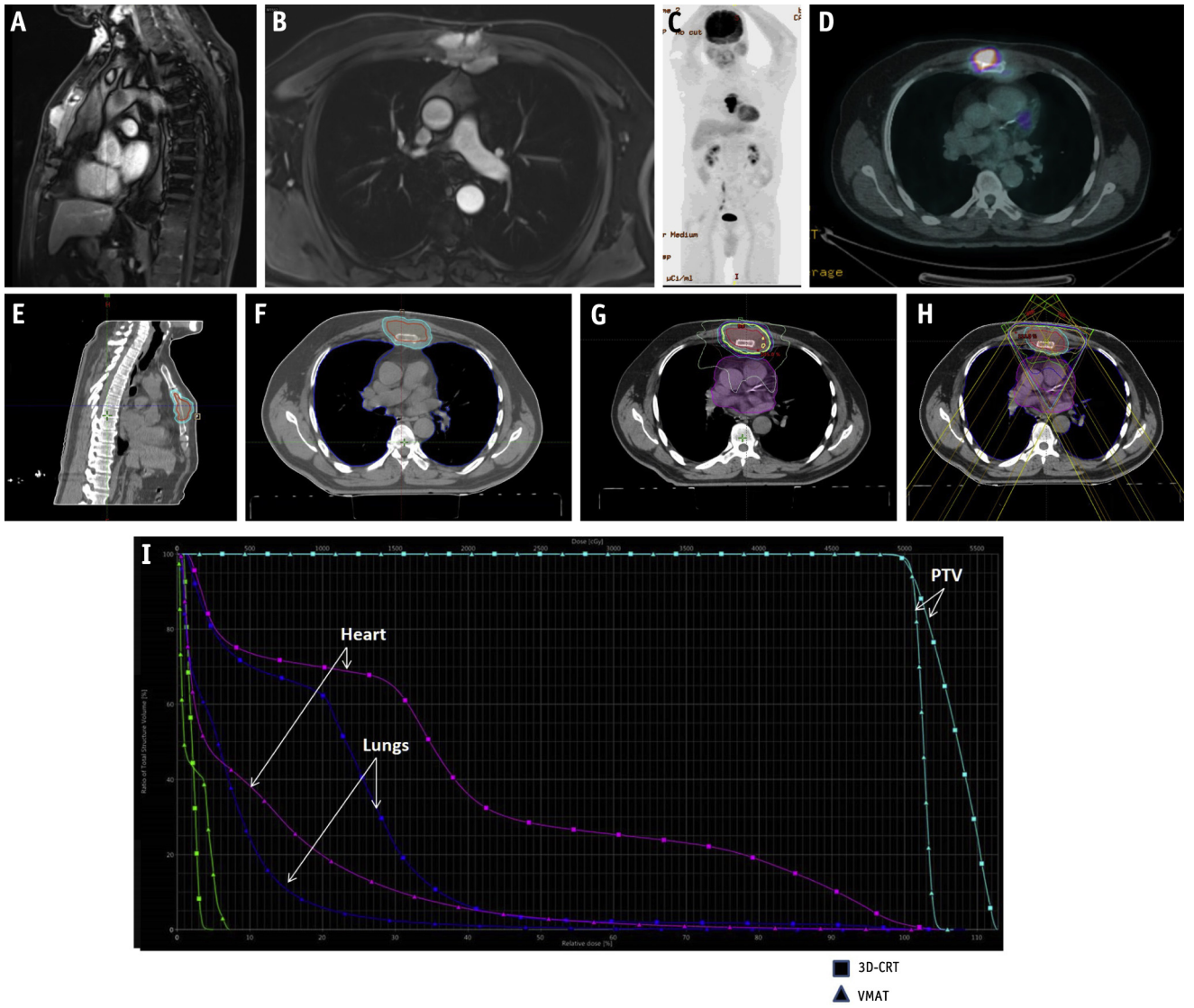

Fig. 3. Solitary bone plasmacytoma in a 67-year-old man with a painful lump of the anterior chest wall. A magnetic resonance imaging scan (T1 images) showed enhancing sternal mass 6 cm × 6 cm × 4.5 cm, in sagittal (A) and axial (B) perspectives. Solitary area of fluoro-deoxyglucose -avid tumor on a positron emission tomography scan, maximum intensity projection image (C) and axial image (D). The clinical target volume was determined from magnetic resonance and positron emission tomography images, with a 1-cm expansion for the planning target volume (PTV), in sagittal (E) and axial (F) perspectives. Definitive radiation therapy with a total dose of 50 Gy in 25 fractions comparison with volumetric arc therapy (VMAT) (G) and 3D conformal (H) techniques, and VMAT was chosen as it gave a superior conformal coverage of the planning target volume, and substantial reduction in doses to the heart and lungs (mean heart dose of 5.7 Gy vs 19.9 Gy; and mean lung dose of 3.7 Gy vs 10.8 Gy), as illustrated in the dose volume histogram (DVH) (I).

Unlike SP, which requires doses in the range of 35 to 50 Gy to obtain durable local control (≥85% at 10 years), lower doses of RT are sufficient to obtain a clinical benefit in patients with symptomatic bony lesions from MM. A retrospective study of 172 patients with MM investigated the most effective RT schedule for patients affected with spinal cord compression from vertebral body disease (55). The authors compared a short course (8 Gy in 1 fraction; 20 Gy in 5 fractions) with a longer course (30 Gy in 10 fractions, 37.5 Gy in 15 fractions, and 40 Gy in 20 fractions) with respect to improvement of functional outcome for at least 6 months or until death. The long course resulted in higher rates of improvement in motor function, when compared with the short course both at 6 (67% vs 43%, $P = .043$) and 12 months (76% vs 40%, $P = .003$). Yet, the functional outcomes were analogous among the 3 long course schedules at the same time points. A randomized trial that compared 30 Gy in 10 fractions with 8 Gy in 1 fraction for symptomatic bone lesions in 101 myeloma patients found similar response rates for pain relief, but the quality of life improvement with RT when measured with the European Organization for Research and Treatment's QLQ-C30 symptom and function

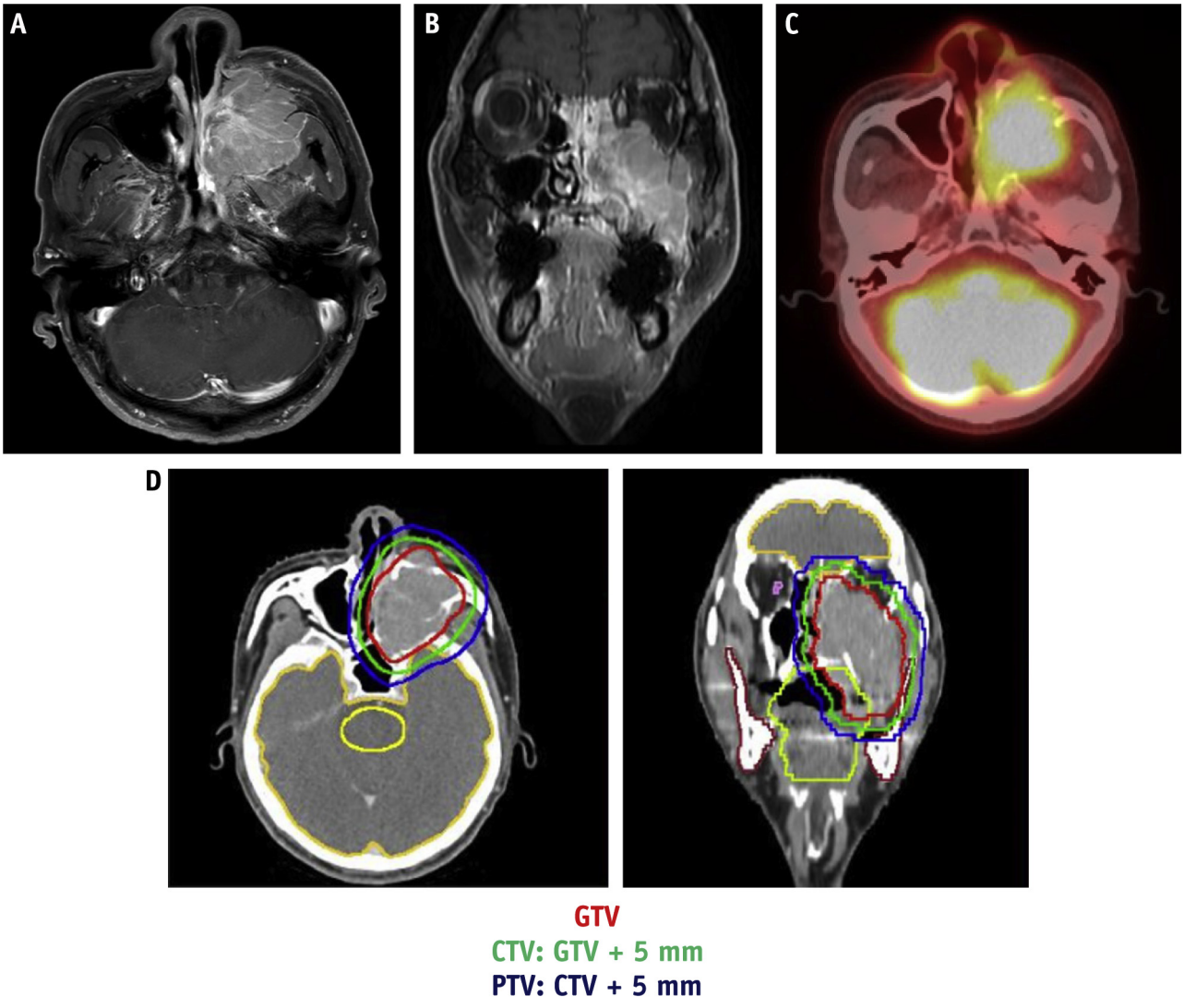

Fig. 4. Solitary extramedullary plasmacytoma in a 57-year-old man, presenting with nasal obstruction, swelling of left cheek and proptosis of the left eye. On examination the tumor infiltrated into the left upper buccal alveolar sulcus. A magnetic resonance imaging scan (T1-weighted images) showed an enhancing mass occupying much of the left maxillary sinus, with infiltration into the left nasal cavity, ethmoid sinus, orbit, and left palate/buccal areas, shown in axial (A) and coronal (B) perspectives. The disease was intensely fluoro-deoxyglucose-avid on a positron emission tomography scan (C). Definitive radiation therapy (RT) with tomotherapy, with the gross tumor volume (red), clinical target volume (green), and planning target volume (blue) illustrated in axial and coronal perspectives (D). Total dose 45 Gy in 25 fractions, isodose distributions in axial, coronal, and sagittal perspectives (E). Post-treatment positron emission tomography scan (1 month after completion of RT) showed residual mass in the maxillary sinus, but complete metabolic response (F), and further improvement with only mucosa thickening on a computed tomography scan 20 months after completion of RT (G). (A color version of this figure is available at www.redjournal.org.)

scales was only seen with the fractionated regimen (56). Another prospective randomized trial (57) compared a shorter (20 Gy in 5 fractions) and a longer course (30 Gy in 10 fractions) regimen in patients affected with metastatic epidural spinal cord compression from different tumor types and showed no differences both in terms of 6-month functional outcomes (57.5% vs 60%, respectively) and local control (75.2% vs 81.8%, respectively) between the 2 arms. Of importance, the results of this trial were considerably limited by the absence of a stratification of the clinical endpoints for the different tumor histologies (58). A post-hoc analysis (57) was thus conducted and confirmed comparable outcomes between the 2 arms also in the subgroup of patients affected with hematologic malignancies (mainly myeloma), although the limited numbers (only 16/203 patients enrolled in the trial were affected with myeloma/lymphoma) do not allow a definitive conclusion.

Based on the results of these studies and consensus opinion of the ILROG panel, the following dose/fractionation guidelines are recommended for palliative RT in MM:

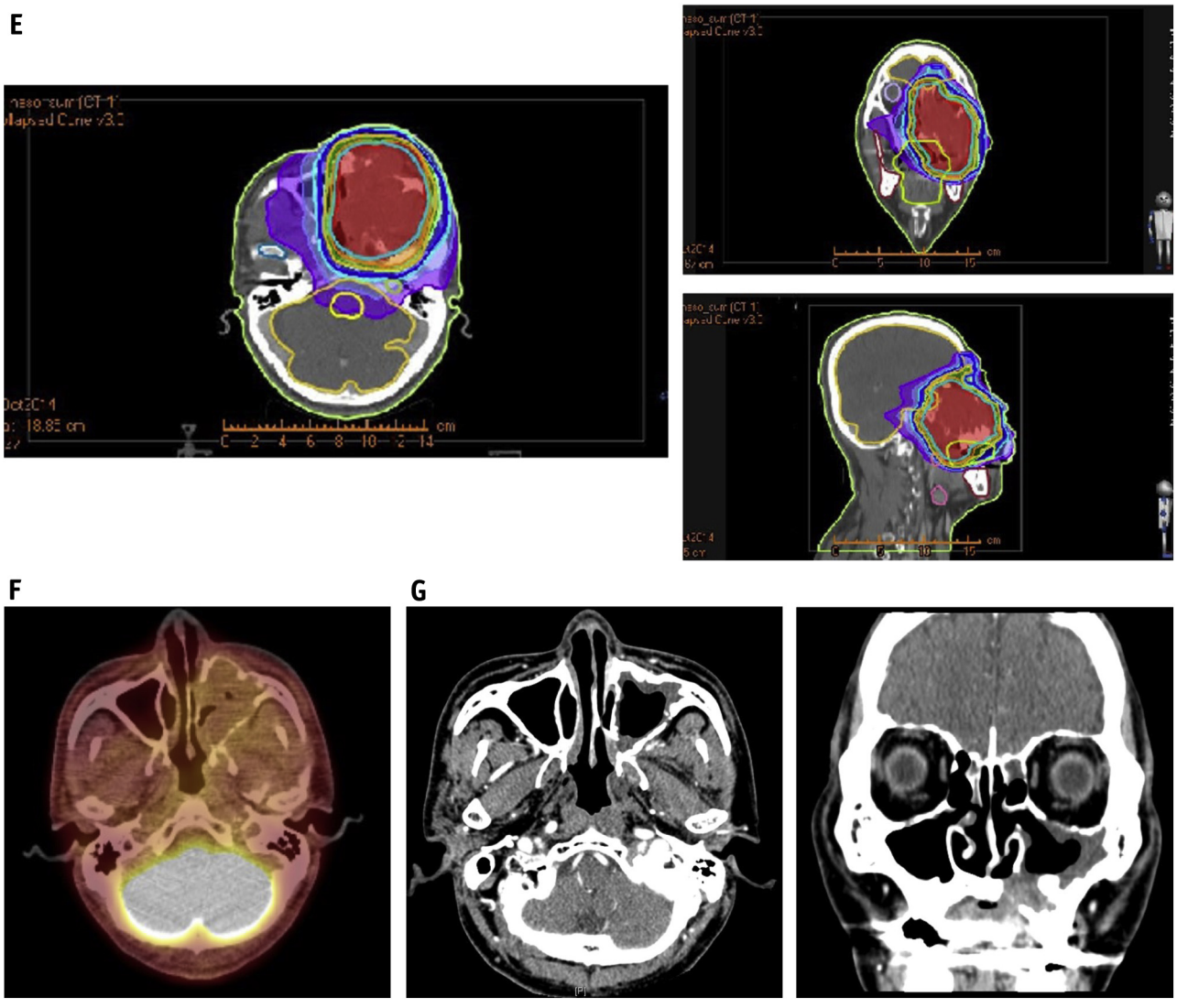

Fig. 4. (*continued*)

- For bony sites, where the goal is limited to symptom relief: a hypofractionated regimen with a total dose of 8 to 30 Gy (eg, 8 Gy in 1 fraction, 20 Gy in 5 daily fractions, or 30 Gy in 10 daily fractions, delivered as 5 fractions per week). A single 8 Gy fraction is preferred for bone disease in patients with poor prospects for survival.
- Alternatively, conventional fractionation: 20 to 30 Gy in 10 to 15 daily fractions, at 5 fractions per week. This approach may be preferred if RT volumes are large or for retreatment.
- For epidural disease with spinal cord compression, or a bulky mass, when durable local control is desired: 30 Gy in 10 to 15 daily fractions, at 5 fractions per week (Fig. 5).
- For cases with nerve root or spinal cord compression: coverage with glucocorticoids is recommended (eg, dexamethasone 4 mg qid, prednisone 50-75 mg bid, or equivalent) and can also be considered to prevent pain flare (eg, dexamethasone 4 mg bid).

In practice, the use of palliative RT for symptomatic lesions should be used judiciously and should be limited as much as possible to spare the patient's residual marrow function. Dose constraints for sensitive organs at risk must be respected. Current novel agents (eg, bortezomib, ixazomib, carfilzomib, lenalidomide, thalidomide, pomalidomide, daratumumab) provide higher rates of clinical complete response and progression-free survival and, together with bisphosphonates, possibly decrease the need for local therapies. However, MM remains an incurable disease; with patients living longer (51), RT is frequently needed to palliate symptomatic lesions. Some concerns still exist regarding the potential toxicity following concurrent chemotherapy and RT, specifically in terms of sensitization of normal tissue toxicity or depletion of the bone marrow reserve. Few retrospective studies have investigated this issue. Shin et al have shown no differences in terms of hematologic toxicity between patients treated with RT alone and those receiving RT with concurrent "novel agents-based" chemotherapy (59). Combined treatment gave an improved serologic

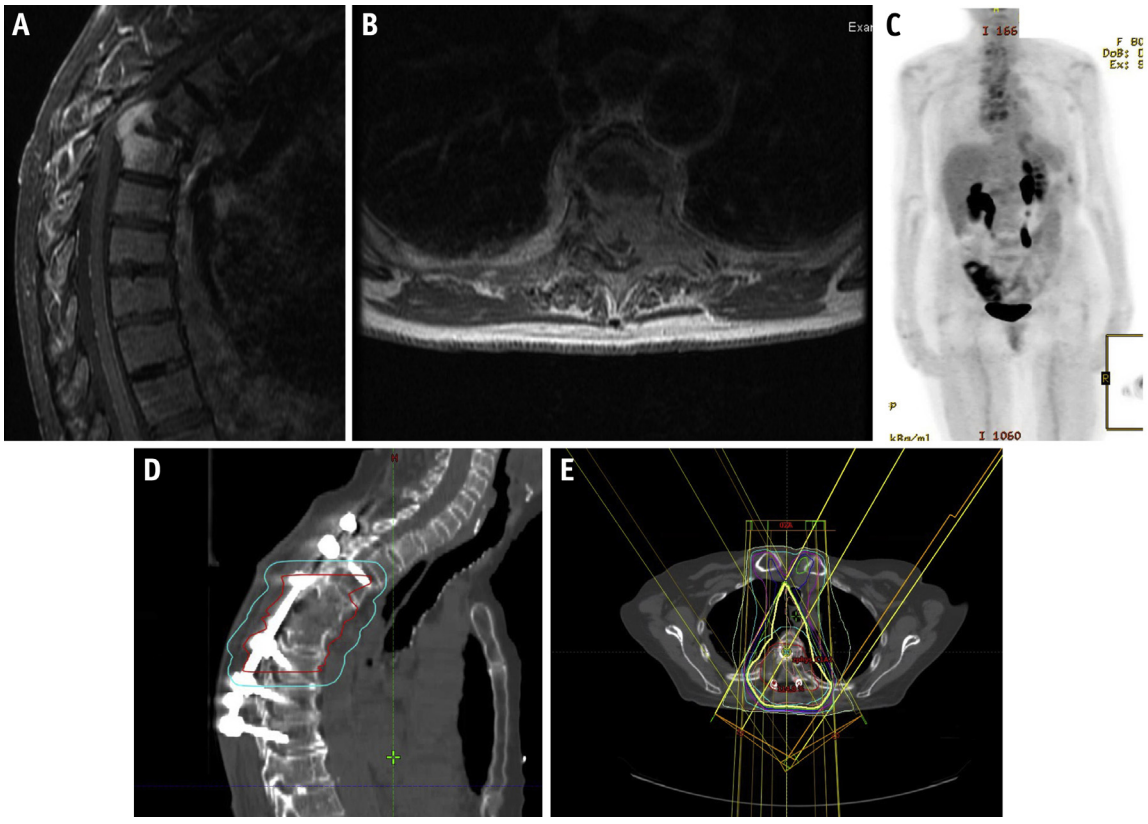

Fig. 5. A 79-year-old woman with acute back pain and rapidly progressive leg weakness with urinary retention was found to have spinal cord compression at the T5 level on magnetic resonance imaging. T1-weighted sagittal (A) and axial (B) images revealed near total destruction of the T5 vertebral body, with kyphotic deformity, and a soft tissue tumor extending to both T4 and T6 vertebrae. Enhancing soft tissue tumor at T5 compressed and displaced the spinal cord. Urgent surgery was performed, with T5/6 corpectomy, laminectomy, and fusion from T2 to T8. Pathology revealed a plasma cell neoplasm. A fluoro-deoxyglucose–positron emission tomography scan showed postoperative changes from T2 to T8, and no other sites of fluoro-deoxyglucose-avid disease (C). Serum M-protein was detected with IgG of 789 mg/dL, and a bone marrow biopsy showed 12% clonal plasma cells. A diagnosis of multiple myeloma was established. Postoperative radiation therapy was given to offer optimal local control, and the clinical target volume (red) was based on the preoperative extent of the local disease on magnetic resonance imaging, with a 1-cm isotropic expansion for the planning target volume (light blue) (D). Note that the full extent of the surgical hardware need not be covered. The prescribed dose was 30 Gy in 10 fractions with a 3D conformal technique (E), as a palliative treatment. The patient subsequently started on systemic chemotherapy. (A color version of this figure is available at www.redjournal.org.)

response (decrease of monoclonal protein) with a trend to significance ($P = .08$). However, one should be cautious of a combination of abdominal RT and concurrent bortezomib owing to case reports of gastrointestinal toxicity (60, 61), although larger studies of bortezomib in combination with RT to the brain or other metastatic sites (in solid tumors) indicate that it is generally safe aside from predictable myelosuppression (62, 63).

As systemic therapy has improved in the last 2 decades, with patients surviving longer, there has been an emergence of disease spread to the central nervous system (CNS) (64-66). This is still an infrequent observation but presents a challenging clinical problem. Patients can have parenchymal brain involvement with or without leptomeningeal disease. Such patients are often heavily pretreated, and may have comorbidities and other complications of prior therapies such as neuropathy or thrombotic events. The prognosis of patients with CNS myeloma is extremely poor with expected median survival of 2 to 6 months and 1 year survival of ~20% (64-66). One series of 37 patients indicated that when appropriate, CNS irradiation either with whole brain RT or, if the systemic myeloma disease is well-controlled, craniospinal radiation can lead to improved CNS control in the short term, and possibly long-term survival, compared with other treatment approaches (66).

RT Volume and RT Planning for SP and MM

Determination of gross tumor volume

Using the primary imaging of untreated lesions, the gross tumor volume (GTV) should be outlined on the simulation study and is always part of the clinical target volume

(CTV). When feasible, fusion of the primary imaging (eg, PET/CT or MRI) with the simulation study can be helpful to define the GTV. Field placement practices based on anatomic landmarks are obsolete (eg, fields to include 1 or 2 normal vertebral bodies above and below the grossly involved vertebra) and should not be used.

Determination of CTV

By definition, the CTV encompasses the original GTV and suspected microscopic subclinical disease. In the setting of definitive RT for SP, it is reasonable that the CTV includes the GTV plus a margin of 0.5 to 3 cm expanded in all directions, respecting anatomic boundaries. An axial GTV to CTV expansion of 0.5 to 1 cm may be appropriate for potential microscopic extension in soft tissues (eg, in the head and neck area; see Figs. 2 and 4). However, for a long bone site the proximal and distal expansion should be increased to 2 to 3 cm depending on the availability of accurate imaging with MRI and PET/CT. Adjacent normal structures that are clearly uninvolved or at low risk of subclinical disease, should be excluded from the CTV. In outlining the CTV, the following points should be considered:

- Quality and accuracy of imaging (ideally MRI and PET information taken into account)
- Concerns of changes in volume since imaging
- Local spread of disease (MRI very useful)
- Potential subclinical involvement (eg, potential nodal involvement with head and neck sites)
- Adjacent organs and constraints

Special circumstances for outlining the CTV are discussed below.

Whole bone irradiation for SBP

When there is uncertainty regarding the extent of bone involvement on imaging and when encompassing the whole bone in the CTV is unlikely to add any significant additional morbidity risks, it is acceptable to include the whole bone (eg, the entire vertebral body) in the CTV.

Elective regional nodal irradiation for SEP of the head and neck

Elective nodal irradiation for SEP of the head and neck is controversial. In patients with known regional involvement of the cervical nodes who are to be treated with curative intent, it is reasonable to consider elective nodal irradiation of the uninvolved ipsilateral cervical neck nodes. For SEP involving Waldeyer's ring structures (eg, tonsil, nasopharynx), when optimal imaging is available and shows no involvement of cervical lymph nodes, intentional prophylactic coverage of the nodes is not recommended (Figs. 2 and 4).

Postoperative irradiation for SP

Postoperative irradiation to the surgical bed is indicated for patients with incomplete surgical excision. In the definitive treatment of SP, consideration should also be given to include all surgical hardware within the CTV if there was potential surgical seeding of malignant cells (eg, the full extent of the intramedullary nail used to stabilize a pathologic fracture of the femur). While treatment of the entire femur seems prudent clinically, more data are needed to evaluate this formally. Surgical hardware used to stabilize the spine may not disrupt a plasmacytoma. In this case the hardware will not need to be treated (Fig. 5). In the palliative setting, it is reasonable to omit the surgical hardware from the CTV in order to limit excessive toxicity risks (Fig. 5).

Palliative irradiation in the setting of MM

In the palliative setting, it is reasonable to omit an additional margin from GTV to CTV as it is not critical to cover adjacent subclinical disease in the context of wider systemic disease. Whole bone coverage is generally not required (67). These considerations are particularly relevant in the palliative irradiation of symptomatic plasmacytomas in patients with advanced MM when minimization of toxicity is a clinical priority.

Determination of internal target volume

When expected physiologic movement (eg, respiration) affects the CTV, an additional margin, internal target volume (ITV), should be added to the CTV to account for this movement. The optimal method is to use 4D CT simulation to identify the required ITV margins.

Determination of planning target volume

The planning target volume (PTV) is the volume that takes into account the CTV (or ITV, when relevant) and is expanded to account for setup uncertainties during RT planning and treatment sessions. This margin depends on estimated setup variations that are a function of the immobilization device, body site, and patient compliance. In general, margins for uncertainties should be added quadratically to avoid excessive margins based on the most extreme (and least likely) situations.

Technical considerations/organs at risk

As with most cases requiring RT for hematologic malignancies, the considerations to weigh in choosing various treatment modalities include the following: treatment site, volume, and desired prescription dose. The target volume and nearby organs at risk (OARs) may largely dictate the treatment modality chosen for each individual case. As the location of treatment is heterogeneous and can occur anywhere in the body, only general guidelines are described here. Determining the nearby OARs is always important; these are critical normal structures that can manifest adverse effects from radiation, which are largely dependent

on the total dose and dose per fraction of radiation received (68). The OARs relevant to treatment planning should be outlined on the CT-based simulation study. The dosimetry/physics team should calculate dose-volume histograms, and the plan should be evaluated considering the expected normal tissue complication probability. The objective is to restrict the dose to the OAR to "as low as reasonably achievable" (ALARA principle), rather than a set dose level to keep within traditional tolerance limits. Consideration should also be given to factors such as gender, age, comorbidities of the patient, and previous RT exposure. Some structures, such as the spinal cord, brain stem, cauda equina, optic structures, lung, heart, and kidneys are more critical than others and may therefore require higher prioritization. On the basis of comparative treatment planning (comparison dose-volume histogram) and determination of the priority of the OARs to protect, the radiation oncology team should make a clinical judgment as to which treatment technique to use. In some situations, conventional anteroposterior-posteroanterior beams may be preferred, because the smallest volume of normal tissue would be irradiated with this technique, albeit to the full-prescribed dose. In other situations, more conformal techniques, such as intensity-modulated radiation therapy (IMRT), helical-IMRT, or volumetric arc therapy (VMAT) approaches may offer significantly better sparing of critical normal structures (Figs. 2-4), usually at the cost of a larger total volume of normal tissue irradiated, but to a lower dose (69). Image guidance during RT delivery may offer a clinically appropriate advantage, particularly for treatment sites that are adjacent to critical dose-limiting normal structures. One should take into consideration the cost effectiveness and frequency (daily vs weekly) of image guidance for purposes of small margins with advanced technologies (ie, SP of the head and neck treated with IMRT) or tumor sites that may have changes in target size during RT.

During simulation of a patient with SP/MM of the head and neck, optimal immobilization with a customized 5-point thermoplastic mask should be used to allow for tight CTV to PTV margins (Figs. 2 and 4). Treatment techniques used in the treatment of head and neck cancer (IMRT or VMAT) are often appropriate for SP/MM in the same locations. For example, a case of a localized SP of the head and neck region may require definitive treatment with IMRT or VMAT for highly conformal dose distribution and maximal sparing of adjacent structures (ie, parotid gland, orbit, oral cavity) (Figs. 2 and 4). On the contrary, a MM lesion of the spine may require palliative RT with simple 2D or more complex 3D-comformal RT for a fractionated or hypofractionated treatment course (Fig. 5).

Follow-Up Procedures

Follow-up procedures include clinical assessment, plus serum and urine testing for any persistent M-protein on a regular basis (eg, every 6 months). For patients with SP and a M-protein detectable prior to definitive RT, successful treatment is associated with a disappearance of the M-protein (which may take several months after RT); persistence of the M-protein predicts a very high risk of progression to MM (22, 38, 70). A complete blood count, serum chemistry (calcium and creatinine), and episodic skeletal survey are common practices for surveillance testing to detect progression to MM.

Reimaging is indicated in the response assessment of SP and is best performed 3 to 6 months after therapy, depending on clinical circumstances. In cases of SBP, bony destruction due to the tumor will produce persistent abnormalities on imaging, particularly skeletal x-ray and CT scans. MRI or PET/CT scans are preferred to assess the response of soft tissue components of the tumor and also for SEP. Minimal abnormalities even on MRI can persist for many months following the definitive RT of SP and should not be interpreted as persistent disease. It may take 6 to 8 months for SP to reach maximum response after definitive RT. PET/CT scanning when available can be very useful because a metabolic response is usually observed earlier when persistent abnormalities are seen on routine imaging with CT or MRI (18, 71) (Fig. 4). Periodic reimaging every 4 to 6 months can be considered for any residual tumor mass, until complete response or any residual abnormality remains stable on consecutive scans. It is generally not beneficial to continue to reimage a stable minor residual abnormality unless there are clinical indications to do so.

Future Directions and Conclusions

The combination of novel agents and RT has been underexplored, particularly for bulky plasmacytomas. The addition of adjuvant novel agents to RT, such as proteasome inhibitors or immunomodulatory drugs (eg, lenalidomide), is a theoretically attractive approach, both in enhancing local control and possibly eradicating subclinical disease in patients with SP to prevent the development of systemic MM. Preliminary data suggest feasibility and effectiveness of a combined approach (36, 72). This approach will be under active investigation in the United Kingdom in a phase 3 study, examining the potential role of lenalidomide with dexamethasone in improving progression-free survival (73).

Technological advances may modify the RT strategies in the future. In this regard, spinal radiosurgery may represent an interesting opportunity for highly selected patients affected with MM (eg, in a reirradiation scenario). A preliminary cooperative experience reported excellent clinical outcomes after a single fraction of 16 Gy in a population of 38 MM patients (74). These interesting results need to be confirmed in a larger cohort and should not be considered standard practice in radiation-naïve patients (as standard fractionation regimens result in excellent outcomes) but

could be useful in selected situations such as retreatment (salvage therapy for patients with prior RT). Participation in clinical trials is encouraged.

RT can also be considered for use as "systemic" therapy adjunct to control MM, eg, in the setting of total body irradiation (TBI) and stem cell transplant. Although TBI has been commonly used in the past as part of the preparatory regimen for autologous hematopoietic stem cell transplantation, it was shown to be associated with higher toxicity when compared with melphalan alone (75). Therefore, TBI is now less commonly used for MM. The advent of newer RT techniques is currently being explored; eg, total marrow irradiation has been found to be a safe and feasible technique in patients with MM (76, 77).

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