Guidelines on the diagnosis and management of solitary plasmacytoma of bone and solitary extramedullary plasmacytoma

Most patients with plasma cell neoplasia have generalized disease at diagnosis, i.e. multiple myeloma (MM). However, a minority (<5%) of patients with plasma cell malignancies present with either a single bone lesion, or less commonly, a soft tissue mass, of monoclonal plasma cells: solitary bone plasmacytoma (SBP) or extramedullary plasmacytoma (SEP). SBP has a high risk of progression to MM and on magnetic resonance imaging (MRI) examination at least 25% of patients with an apparent solitary lesion have evidence of disease elsewhere (Moulopoulos *et al*, 1993). In contrast, SEP is nearly always truly localized and has a high cure rate with local treatment.

The diagnosis and management of patients with solitary plasmacytoma requires the same range of clinical and laboratory expertise as for patients with MM (UK Myeloma Forum, 2001). The primary treatment for most patients will be radiotherapy, but surgery may also be required, where close liaison among the haematologist, radiotherapist and surgeon is crucial for planning optimum care.

Methods

A literature search was performed by a professional librarian using MEDLINE and EMBASE from 1996 to March 2002. A search was made for randomized-controlled trials involving plasmacytoma, papers where plasmacytoma was the major focus of the paper and reviews where plasmacytoma was the major focus. The literature was then reviewed by the subgroup of the Guidelines Working Group of the UK Myeloma Forum. Levels of evidence and grades of recommendation are shown in Table I. SBP and SEP are rare diseases and most of the evidence relates to retrospective data from patient series collected over long periods of time. Very few formal clinical trials have been performed. The majority of the recommendations given are therefore based on consensus of expert opinion.

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Solitary bone plasmacytoma

Context

Epidemiology and clinical features. Solitary bone plasmacytoma has a male:female ratio of 2:1, with a median age of 55 years and primarily affects the axial skeleton especially the vertebrae (see Table II) (Dimopoulos *et al*, 2000). Malignant bone tumours of the spine are extremely rare (<0·05% of primary neoplasms). Solitary plasmacytoma is the commonest separate entity within this group, accounting for approximately 30% of the total (McLain & Weinstein, 1989). These tumours occur in the spine twice as often as other bony sites (Chang *et al*, 1994). The commonest symptom is pain but it can also present with cord or root compression. Involvement of the base of the skull can present with cranial nerve palsies (Vaicys *et al*, 1999; Vijaya-Sekaran *et al*, 1999). Localized amyloidosis can be a feature of both SBP and SEP (Pambuccian *et al*, 1997; Nagasaka *et al*, 2001). As well as the appropriate blood and urine tests (see below), specific imaging of the spine is required and best achieved by MRI ± computed tomography (CT). Bone scans are unreliable. Biopsy is usually possible percutaneously, guided either by fluoroscopy or CT.

The presence of a monoclonal paraprotein (M protein) has been reported in 24–72% of patients in different series (Dimopoulos *et al*, 2000). The frequency probably depends on the level of sensitivity of the tests used. In a recently reported series of 60 patients from the MD Anderson Hospital presenting between 1995 and 2000 (Wilder *et al*, 2002), a serum or urinary paraprotein was detectable in 43 patients (62%) by routine electrophoresis or immunofixation/immunoelectrophoresis. However, the levels of paraprotein were generally low. Of the 37 patients who had a serum paraprotein, only 11 had levels over 10 g/l and the highest level was 22 g/l. In the six patients who only had Bence Jones protein in the urine, total daily excretion of urinary-free light chain was below 100 mg/d in all patients.

Natural history and prognosis. The majority of patients with apparent SBP develop myeloma, with a median time to progression of 2–4 years (Table II). The median overall survival in different series varies from 7·5 to 12 years (Dimopoulos *et al*, 2000). Most reported series extend over a long time period and the majority of included patients have

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Table I. Levels of evidence and grades of recommendation.

Levels of evidence	
Ia	Evidence obtained from meta-analysis of randomized-controlled trials
Ib	Evidence obtained from at least one randomized-controlled trial
IIa	Evidence obtained from at least one well-designed, non-randomized study, including phase II trials and case ± control studies
IIb	Evidence obtained from at least one other type of well-designed, quasi- experimental study, i.e. studies without planned intervention, including observational studies
III	Evidence obtained from well-designed, non-experimental descriptive studies. Evidence obtained from meta-analysis or randomized-controlled trials or phase II studies which is published only in abstract form
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.
Grades of recommendation	
Grade A	
Evidence level Ia, Ib	
Recommendation based on at least one randomized-controlled trial of good quality and consistency addressing specific recommendation	
Grade B	
Evidence level IIa, IIb, III	
Recommendation based on well-conducted studies but no randomized-controlled trials on the topic of recommendation	
Grade C	
Evidence level IV	
Evidence from expert committee reports and/or clinical experiences of respected authorities	

Table II. Clinical features of solitary bone plasmacytoma (SBP) and extramedullary plasmacytoma (SEP).

	SBP	SEP
Age (years), median	55	55
M:F	2:1	3:1
Predominant site	Axial skeleton, especially vertebrae	Head and neck
% with M protein	60	<25
% developing MM	>75	<30
% survival at 10 years	40–50	70

Figures based on data of Frassica *et al* (1989), Bolek *et al* (1996), Dimopoulos *et al* (2000), Galieni *et al* (2000) and Wilder *et al* (2002).

not had MRI scans. These patients will therefore include a proportion of patients with asymptomatic myeloma. The progression-free and overall survival in patients with SBP may improve as MRI examination becomes an established part of the staging criteria for the diagnosis and patients with early MM are excluded.

Quoted adverse prognostic features for progression to MM include low levels of uninvolved immunoglobulins, axial disease, older age, lesion size >5 cm and persistence of the M protein after treatment (Bataille & Sany, 1981; Holland *et al*, 1992; Tsang *et al*, 2001). However, these adverse prognostic features have not been consistent between series (Chak *et al*, 1987; Frassica *et al*, 1989; Bolek *et al*, 1996; Liebross *et al*, 1998). A recent multivariate analysis of prognostic factors in a series of 60 patients from the MD Anderson Hospital (most of whom were not staged by MRI) concluded that persistence of M protein for more than 1 year after radiotherapy was the only independent adverse prognostic factor (Wilder *et al*, 2002). The paraprotein disappeared in 13 patients and persisted in 32, while 15 patients had non-secretory disease. At a median follow-up of 7·8 years, only one of 13 patients with resolution of the paraprotein progressed to MM while over 90% of patients with persistent paraprotein had progressed. Most patients with persistent M protein progressed to MM within 2 years of treatment. Age, tumour size and level of paraprotein at diagnosis had no independent prognostic value. In this series, patients with non-secretory disease appeared to do less well than those with a paraprotein that disappeared after radiotherapy.

As already indicated, it is likely that many of the patients with apparent SBP who progress actually have disseminated disease at presentation. MRI examination of the spine can detect occult disease in approximately 26% of patients with apparent SBP (Moulopoulos *et al*, 1993; Wilder *et al*, 2002). Conversely, a negative MRI of the spine is a good prognostic feature. Liebross *et al* (1998) showed that in a series of 15 patients with a spinal plasmacytoma who did not have a positive MRI examination, progression to MM occurred in seven of eight patients where MRI had not been performed as opposed to one of seven with a negative MRI of spine (patients with other lesions on MRI were considered to have MM). Positron emission tomography (PET scanning) has recently been evaluated in the staging of patients with myeloma and plasmacytoma (Orchard *et al*, 2002; Schirrmeister *et al*, 2002). PET scanning, like MRI, appears to be useful in detecting occult disease in patients with apparent solitary SBP. Those patients with SBP who do subsequently develop MM have a relatively good prognosis. Liebross *et al* (1998) reported that their patients with SBP who progressed to MM were characterized by low tumour mass, 77% response rate to chemotherapy and a median survival from progression of over 5 years. Patients progressing to MM should be treated according to the British Committee for Standards in Haematology (BCSH) guideline on the management of MM (UK

Myeloma Forum, 2001). In addition, patients presenting as SBP but found upon MRI scan to have more extensive disease should be considered as having MM and treated accordingly (see below).

Diagnosis and investigation of SBP

Diagnostic criteria. Recommended diagnostic criteria are summarized in Table III. Based on the data discussed above, the following criteria are recommended:

- single area of bone destruction due to clonal plasma cells;
- histologically normal marrow aspirate and trephine (<5% plasma cells);
- normal results on skeletal survey, including radiology of longbones;
- no anaemia, hypercalcaemia or renal impairment due to plasma cell dyscrasia;
- absent or low serum or urinary level of monoclonal immunoglobulin (level of >20 g/l suspicious of MM, see above);
- no additional lesions on MRI scan of the spine (see below for criteria of involvement).

Pathology review. Solitary bone plasmacytoma is generally diagnosed by biopsy or fine needle aspiration. Percutaneously guided biopsy of the spine is usually possible either by fluoroscopy or CT. As these tumours are rare, pathology review by a histopathologist with a special interest in either bone tumours or lymphoproliferative disorders is strongly recommended.

Further investigations. The following investigations should be performed in all patients:

Table III. Recommended diagnostic criteria for solitary bone plasmacytoma (SBP) and extramedullary plasmacytoma (SEP).

Solitary bone plasmacytoma
Single area of bone destruction due to clonal plasma cells
Histologically normal marrow aspirate and trephine
Normal results on skeletal survey, including radiology of long bones
No anaemia, hypercalcaemia or renal impairment due to plasma cell dyscrasia
Absent or low serum or urinary level of monoclonal immunoglobulin
No additional lesions on MRI scan of the spine
Solitary extramedullary plasmacytoma
Single extramedullary mass of clonal plasma cells
Histologically normal marrow aspirate and trephine
Normal results on skeletal survey, including radiology of long bones
No anaemia, hypercalcaemia or renal impairment due to plasma cell dyscrasia
Absent or low serum or urinary level of monoclonal immunoglobulin

- full blood count;
- biochemical screen including electrolytes and corrected calcium;
- serum immunoglobulin levels;
- serum and urine protein electrophoresis and immunofixation;
- full skeletal survey, including standard X-rays of the skeleton including lateral and anteroposterior cervical, thoracic and lumbar spine, skull, chest, pelvis, humeri and femora (UK Myeloma Forum, 2001);
- MRI of thoracic and lumbar spine;
- bone marrow aspirate and trephine.

Additional investigations may be useful in selected patients, including

- MRI of pelvis, proximal femora and humeri;
- immunophenotyping and molecular assessment of bone marrow plasma cells;
- PET scanning.

The role of β2 microglobulin in the diagnosis and management of SBP has not been established. There are, at present, no data on the use of the serum-free light chain assay in SBP.

MRI examination. There are no reported guidelines to define involvement on an MRI scan in the context of apparent SBP. However, the MRI appearances in MM have been well described (Baur *et al*, 2002). The presence of one or more foci of abnormal signal intensity [low on T1 weighted imaging and high on T2 weighted or STIR (Short TI Inversion Recovery) images], which enhance after the administration of paramagnetic contrast in the absence of known recent compression fractures, other primary malignancy or typical characteristics of benign or malignant primary bone tumours, is considered evidence of distant involvement in patients with apparent SBP (M. Dimopoulos, personal communication).

Treatment of SBP

Radiotherapy. This subject has recently been reviewed (Hu & Yahalom, 2000). Radical radiotherapy is the treatment of choice for SBP. In common with other rare tumours, the evidence base for treatment is largely composed of retrospective studies of small numbers of patients. Progression to MM is common, despite high local control rates of 83–96% achieved with moderate doses of radiotherapy (Mayr *et al*, 1990; Holland *et al*, 1992; Bolek *et al*, 1996; Liebross *et al*, 1998; Tsang *et al*, 2001).

Data on dose–response relationships are weak in most series, due to relatively low patient numbers and narrow range of doses used. Mendenhall *et al* (1980) recommended a minimum dose of 40 Gy following a dose response analysis based on a review of the literature including 81 patients. They reported a 6% local failure rate in patients with SBP treated with doses of 40 Gy or above, in contrast to 31% for doses

below 40 Gy. Some centres prefer to use higher doses of 45–50 Gy (Mayr *et al*, 1990; Liebross *et al*, 1998), but there is little evidence for a dose response curve above 40 Gy and sporadic local failures have been reported after doses of 50–60 Gy (Mayr *et al*, 1990; Liebross *et al*, 1998). Tsang *et al* (2001) reported the Princess Margaret Hospital experience of 32 patients with SBP treated between 1982 and 1993, and concluded that there was no convincing dose–response relationship above 35 Gy. They reported that tumour bulk was the most significant factor influencing local control with 100% local control for SBP of 5 cm or less and only 38% for SBP >5 cm. Their data suggest that bulky SBP of >5 cm requires a higher dose or, perhaps, combined modality treatment for effective local control. This finding is supported by several other reports (Mayr *et al*, 1990; Holland *et al*, 1992). Based on the evidence above, a dose of 40 Gy in 20 fractions is recommended for SBP of 5 cm or less. For SBP >5 cm, a higher dose of up to 50 Gy in 25 fractions should be considered. An alternative strategy for tumours >5 cm is preliminary chemotherapy followed by radiotherapy. This is theoretically attractive but there is little published evidence to support it.

The choice of clinical target volume for radiotherapy is also controversial. Some authors recommend that the entire bone involved should be treated (Mayr *et al*, 1990). The rationale for this is largely based on marginal recurrences in retrospective series treated before modern imaging. MRI scanning accurately delineates bone, bone marrow and soft tissue extent of SBP for radiotherapy planning. Several recent series report excellent local control rates following irradiation of the tumour visualized on MRI scan with a margin, rather than the entire bone involved (Jyothirmayi *et al*, 1997; Liebross *et al*, 1998; Tsang *et al*, 2001). The clinical target volume should include tumour that is visible on MRI with a margin of at least 2 cm. For small bones, such as vertebrae, this will include the entire bone involved, together with one uninvolved vertebra above and below. For larger bones, the clinical target volume will not necessarily include the entire bone, as this would involve unnecessary irradiation of normal tissues.

Assessment of response following radiotherapy depends upon changes in levels of monoclonal protein, resolution or progression of symptoms and evidence of new disease on imaging. Patients whose monoclonal protein disappears with treatment represent a category with a high likelihood of cure (see above) while many of those with persistent paraprotein after 1 year will develop MM. In contrast, post-treatment residual abnormalities on imaging are invariable, difficult to assess and do not correlate with outcome (Liebross *et al*, 1998).

In 25–50% of patients the monoclonal protein disappears with radiotherapy. The monoclonal protein usually falls rapidly but the decline can be slow, lasting several years. Paraprotein persistence and level *per se* are not an indication for treatment but these patients should be monitored very carefully for signs of disease progression. Some patients revert to an apparently stable monoclonal gammopathy of undetermined significance (MGUS).

Patients not responding clinically to radiotherapy do not necessarily have residual tumour. They may have persistent symptoms and/or radiological changes as a result of existing bone destruction, while any residual paraprotein may reflect disease at other sites. In these circumstances a repeat biopsy is advisable to clarify the situation.

Recommendations

It is recommended that SBP is treated with radical radiotherapy, encompassing the tumour volume shown on MRI with a margin of at least 2 cm and treating to a dose of 40 Gy in 20 fractions (grade B recommendation, based on level III evidence).

For SBP >5 cm, a higher dose of up to 50 Gy in 25 fractions should be considered (grade C recommendation, based on level IV evidence).

Patients with SBP require careful monitoring to detect progression to MM, possibly 6 weekly for 6 months with extension of clinic appointments thereafter. Assessment of signs and symptoms should be undertaken in conjunction with laboratory investigations (haematology, biochemistry, serum and urine paraprotein estimation) (grade C recommendation, based on level IV evidence).

Patients not responding to radiotherapy (see above) should be treated with chemotherapy. A suggested approach is to follow guidelines for the treatment of MM (UK Myeloma Forum, 2001). In younger patients, this would include high dose therapy and autologous haemopoietic stem cell transplantation (grade C recommendation, based on level IV evidence).

Patients presenting as SBP but found on MRI to have disease at other sites should be considered as having MM and treated accordingly (grade B recommendation, based on level II evidence).

Surgery. Radiotherapy remains the treatment of choice of the primary pathology and surgery is contra-indicated in the absence of structural instability or neurological compromise. However, early diagnosis and referral for a neurosurgical/orthopaedic opinion is advised in most cases with spinal involvement. Due to the development of modern spinal fixation systems over the last decade, surgical treatment is now a viable and successful option for patients who develop pain caused by structural compromise within the vertebra, vertebral instability, neurological compromise or a combination of these. A number of case reports have been published recently supporting this rationale (Durr *et al*, 1997; Kawahara *et al*, 1998; Fang *et al*, 2001).

Loss of structural integrity requires some form of stabilization procedure and this is most frequently performed by posterior pedicle screw instrumentation. In cases of neurological compromise, decompression is also required. Anterior decompressive surgery usually allows best access to the pathology, although some groups advocate a posterior approach to avoid the potential complications which can occur in trans-cavity access, i.e. thoracotomy (Muhlbauer *et al*, 2000).

Due to the high chance of long-term survival in these patients (McLain & Weinstein, 1989), reconstruction of the destroyed anterior column of the spine may be required. Both biological (structural allografts) and mechanical (using expandable cages/spacers) reconstruction have been used. As yet, there are no data to suggest the superiority of either, although from the theoretical point of view, the former seems to be more attractive.

The relatively new technique of vertebroplasty (Dudenay *et al*, 2002), which has been used with success in MM, has not been reported in solitary plasmacytoma. It is contra-indicated in cases of neurological involvement. Treatment of vertebral collapse in solitary plasmacytoma with vertebroplasty is likely to be of limited value given that, in most cases, the degree of vertebral destruction renders the technique unsuitable.

The choice of surgery and approach needs to be tailored to the specific situation of each patient, depending on such variables as site and extent of tumour, general fitness and condition of the patient, and the experience and preferences of the surgeon. Excellent results, in terms of neurological recovery and pain relief, have been reported in small series in the last decade using this rationale (Chataigner *et al*, 1998; Takahashi *et al*, 1998).

It is often recommended that if surgery is required immediately or in the near future, it should be carried out before radiotherapy is commenced. Surgery is more difficult in patients who have received radiotherapy. However, it is important to note that initial surgery may sometimes compromise radiotherapy, e.g. by the placing of metal supports, which may potentially shield areas of disease from effective radiation dose. Close liaison between haematologist, radiotherapist and surgeon is therefore crucial in planning optimum treatment for individual patients.

Recommendations

Radiotherapy remains the treatment of choice for SBP and surgery is contra-indicated in the absence of structural compromise or neurological compromise (grade C recommendation, based on level IV evidence).

Where surgery is required radiotherapy should also be given and the timing of surgery relative to radiotherapy should be determined for each patient (grade C recommendation, based on level IV evidence).

In cases of spinal plasmacytoma, referral for an opinion from an orthopaedic surgeon or neurosurgeon specializing in spinal surgery is advised (grade C recommendation, based on level IV evidence).

Reconstruction of the anterior column may be beneficial (grade C recommendation, based on level IV evidence).

Adjuvant chemotherapy. The role of adjuvant chemotherapy is at present not clearly defined (Abrams & Frassica, 2000; Hu & Yahalom, 2000). The addition of chemotherapy to radiotherapy in the treatment of SBP might be advantageous in improving local control and preventing or delaying progression to MM. Some reports suggest that adjuvant chemotherapy may delay progression to MM (Mayr *et al*, 1990; Holland *et al*, 1992). However, others observed no benefit (Shih *et al*, 1995; Tsang *et al*, 2001). Only one small, randomized-controlled trial has been carried out. This suggested benefit from adjuvant melphalan and prednisolone, given for 3 years after radiotherapy (Aviles *et al*, 1996). After a median follow-up of 8·9 years, 15 of 28 patients in the radiotherapy arm progressed to myeloma (54%) compared with only three of 25 patients (12%) in the combined modality treatment arm ($P < 0{\cdot}01$). Survival between the two groups of patients showed a significant survival advantage for combined modality therapy ($P < 0{\cdot}01$). Although this was a randomized-controlled trial, the number of patients was small. The results therefore need to be confirmed by further studies before concluding that adjuvant chemotherapy is beneficial, particularly in view of concerns about induction of myelodysplasia/secondary leukaemia and drug resistance.

Recommendations

There are insufficient data to recommend adjuvant chemotherapy in SBP.

It may be appropriate to consider adjuvant chemotherapy in patients at higher risk of treatment failure, e.g. those with bulky disease (>5 cm) (grade C recommendation, based on level IV evidence).

Bisphosphonates. The literature search revealed no publications dealing with the role of bisphosphonate therapy in the management of plasmacytoma. There are, as yet, no reported data on the role of bisphosphonates in preventing progression of MGUS, asymptomatic myeloma or SBP. Currently, there is an ongoing Eastern Cooperative Oncology Group trial to explore the efficacy of zoledronate in these settings (Greipp *et al*, 2003); however, at the present time an evidence-based recommendation cannot be made.

Thalidomide. Currently, there is considerable interest in the role of thalidomide in plasma cell dyscrasias. Thalidomide has successfully been used in the treatment of soft tissue plasmacytoma in the context of relapsed MM (Biagi *et al*, 2001), and is currently being explored in the setting of asymptomatic myeloma (Rajkumar, 2003), but there are currently no data on its effect in SBP.

Management of apparent SBP with positive MRI

Patients that present as SBP but are found upon MRI scan to have more extensive disease (i.e. marrow involvement) should be considered as having MM. However, if the plasmacytoma is the only cause of clinical symptoms and there is no other organ involvement it would be appropriate to treat the

plasmacytoma according to the guidelines above and to defer chemotherapy until there are signs of progression, as per the UK Myeloma Forum/British Committee for Standards in Haematology guidelines for asymptomatic/indolent/smouldering myeloma (UK Myeloma Forum, 2001).

Solitary extramedullary plasmacytoma

Context

Solitary extramedullary (soft tissue) plasmacytomas (SEP) are less common than SBP but carry a better prognosis as the majority can be cured by local radiotherapy (Dimopoulos *et al*, 1999). Although SEP can arise throughout the body almost 90% arise in the head and neck, especially in the upper respiratory tract including the nasal cavity, sinuses, oropharynx, salivary glands and larynx (Brinch *et al*, 1990; Wax *et al*, 1993; Susnerwala *et al*, 1997; Liebross *et al*, 1999; Galieni *et al*, 2000). The next most frequent site is the gastro-intestinal tract. A variety of other sites can rarely be involved, including testis, bladder, urethra, breast, ovary, lung, pleura, thyroid, orbit, brain and skin (Cavanna *et al*, 1990; Rubin *et al*, 1990; Matsumiyama *et al*, 1992; Nonamura *et al*, 1992; Wong *et al*, 1994; Adkins *et al*, 1996; Fischer *et al*, 1996; Tuting & Bork, 1996; Emery *et al*, 1999; Muscardin *et al*, 2000; di Chiara *et al*, 2001).

A monoclonal paraprotein is detected in the serum and/or urine in fewer than 25% of patients (Table II). Local recurrence rates of <5% have been quoted after radiotherapy (Liebross *et al*, 1999). The risk of distant relapse appears to be <30%, i.e. significantly less than with SBP (Mayr *et al*, 1990). Progressive disease may present as MM, SBP or soft tissue involvement of lymph nodes, skin or subcutaneous tissues. When distant relapse occurs this tends to be within 2–3 years of initial diagnosis. At least two-thirds of patients survive for >10 years (Brinch *et al*, 1990; Galieni *et al*, 2000).

Diagnosis and investigation of SEP

Diagnostic criteria. CT or MRI scanning is required to delineate the extent of the lesion but the role of MRI scanning of other areas in the staging of SEP has not been evaluated. As there is a low risk of progression to MM in these patients and the role of MRI in the staging of SEP has not been studied, we do not consider MRI of the spine to be necessary for the diagnosis of SEP. Recommended diagnostic criteria are shown in Table III.

Pathology review. For most patients the diagnosis can be established by fine needle aspiration or biopsy (Kumar *et al*, 1997). As these tumours are rare, and can be confused with non-Hodgkin's lymphoma, pathology review by a histopathologist with a special interest in lymphoproliferative disorders is strongly recommended.

Investigations. As noted above, CT or MRI scanning is required to delineate the extent of the lesion but we do not consider MRI of other areas (see above) to be necessary. Other investigations should be as for SBP (see above).

Treatment of SEP

Radiotherapy. Solitary extramedullary plasmacytoma are highly radiosensitive tumours. Local control rates of 80–100% are consistently reported with moderate doses of radiotherapy (Mayr *et al*, 1990; Bolek *et al*, 1996; Jyothirmayi *et al*, 1997; Liebross *et al*, 1998). Radiotherapy dose and anatomical volume should be chosen to minimize early and late side-effects and maximize local control. There is no firmly established dose–response relationship, because of small patient series and low local failure rates. Tsang *et al* (2001) achieved local control in 13 of 14 (93%) of patients with 35 Gy. The only failure was in a patient with a large primary tumour >5 cm. Similarly, Jyothirmayi *et al* (1997) achieved local control in six of seven patients with 35–45 Gy (median dose 40 Gy in 20 fractions). The only failure was in a patient with an extensive nasopharyngeal tumour. No dose–response relationship was observed. Holland *et al* (1992) also reported poorer local control in tumours >5 cm and similarly observed no evidence of a radiation dose–response effect over a dose range of 16·11–62 Gy (median dose 46·1 Gy). Several series report 100% local control rates. Bolek *et al* (1996) reported 100% local control in 10 patients with doses ranging from 9 to 50 Gy (median dose 45 Gy) and concluded by recommending a dose of 40 Gy in 20 fractions. Shih *et al* (1995) reported on 10 patients with SEP, seven of whom were treated by radiotherapy, using doses of 47–65 Gy. Local control was achieved in all the irradiated patients, raising the possibility that local control could have been achieved with lower radiation doses.

The optimal radiation dose therefore appears to be in the range of 40–50 Gy. SEP <5 cm have an excellent chance of local control with radiation doses in the region of 40 Gy in 20 fractions, whereas there is a higher risk of local failure in tumours >5 cm, which require a higher dose in the region of 50 Gy in 25 fractions.

The optimal radiotherapy target volume is similarly controversial. SEP arising in the upper gastro-intestinal or respiratory tract (>80% of cases) metastasize to cervical lymph nodes in 10–40% of cases (Susnerwala *et al*, 1997; Hu & Yahalom, 2000). The inclusion of draining cervical nodes in the radiation fields significantly adds to acute and late morbidity, especially xerostomia, which may not fully recover. Excellent local control rates are reported when the cervical nodes are electively included (Bolek *et al*, 1996). However, similarly good results are also reported from series in which the cervical nodes are only included if clinically involved. Tsang *et al* (2001) irradiated the primary site alone, except in patients whose primary site was in the lymphatic tissue of Waldeyer's ring, when the first echelon (level) cervical nodes

were included. There were no cervical node failures in 14 patients. Jyothirmayi *et al* (1997) irradiated the primary site only in seven patients and reported no cervical node relapses. Susnerwala *et al* (1997) treated the primary site only in 23 patients and only included the cervical nodes in two patients with clinical cervical node involvement. Again, no lymph node failures occurred. In contrast, Mayr *et al* (1990) reported cervical node failures in two of 11 patients treated to the primary site only and recommended elective cervical node irradiation.

In view of the morbidity of cervical nodal irradiation and the high local control rates reported without it, the balance of evidence favours a policy of treating the primary site with a margin and including the cervical nodes only if clinically involved, or regarded as at high risk, as in primary sites involving Waldeyer's ring.

Recommendations

Solitary extramedullary plasmacytoma should be treated by radical radiotherapy encompassing the primary tumour with a margin of at least 2 cm (grade B recommendation, based on level III evidence).

The cervical nodes should be included if involved. The first echelon cervical nodes should be included in SEP of Waldeyer's ring (grade B recommendation, based on level III evidence).

For SEP up to 5 cm a radiotherapy dose of 40 Gy in 20 fractions is recommended.

For bulky SEP of >5 cm, a higher dose of up to 50 Gy in 25 fractions is recommended (grade B recommendation, based on level III evidence).

Surgery. The majority of SEP occur in the head and neck. Surgery is generally not required for diagnosis. Radical surgery with curative intent is a generally mutilating procedure that is not indicated as the tumours are generally highly radiosensitive and the majority of patients are cured with radiotherapy. For patients with SEP in other areas complete surgical removal should be considered.

A detailed review of the literature by Alexiou *et al* (1999) compared the outcome of patients treated with surgery alone, radiotherapy alone, or combined surgery and radiotherapy. They found reports of 714 cases involving the upper aerodigestive tract (UAD) and 155 cases in other body regions (non-UAD). Most of the latter patients were treated with surgery alone (55·6%) or combined modality treatment (19·8%) and only 11% were treated with radiotherapy alone. The risk of recurrence was the same for the three treatment approaches. It is not clear whether the patients that received a combined approach did so because of incomplete surgical removal.

On the contrary, most of the patients with SEP in the UAD were treated with radiotherapy alone (44·3%) or combined radiotherapy and surgery (26·9%); surgery alone was used in 21·9%. Overall and recurrence-free survival were better in those treated with combined therapy ($P = 0{\cdot}0027$). They concluded that patients with UAD plasmacytoma might benefit from a combined approach. However, this review is somewhat difficult to interpret, as it spans almost a century (from 1905 to 1997) and radiotherapy was not available in any meaningful form for at least half of this period. Furthermore, there are likely to have been significant differences between the patients treated by the different modalities.

There is therefore no good evidence that surgery offers any additional benefit over radiotherapy alone in patients with SEP of the head and neck. Radiotherapy alone is curative in the vast majority of patients. However, if patients have been treated by primary surgery, radiotherapy would only be required in patients with inadequate surgical margins. In contrast to SBP, radiotherapy can be used following surgery without compromise as metal supports are not used in this context.

Recommendations

Radiotherapy alone is the treatment of choice for head and neck SEP (grade B recommendation, based on level III evidence).

Radical surgery should be avoided in head and neck SEP (grade C recommendation, based on level IV evidence).

For SEP at other sites complete surgical removal should be considered if feasible (grade B recommendation, based on level III evidence).

Patients with involved surgical margins should receive adjuvant radiotherapy (grade C recommendation, based on level IV evidence).

No recommendation for adjuvant radiotherapy can be made for patients who have undergone complete surgical excision with negative margins.

Adjuvant chemotherapy. There is no published evidence on the role of adjuvant chemotherapy in the treatment of SEP. It may have a role in selected high-risk patients. Susnerwala *et al* (1997) suggested a higher failure rate in 'high grade' tumours using the MM grading criteria of Bartl *et al* (1987). Tsang *et al* (2001) and Holland *et al* (1992) suggest that tumours >5 cm are at higher risk of failure.

Recommendations

Adjuvant chemotherapy should be considered in patients with tumours >5 cm and those with high grade tumours (grade C recommendation, based on level IV evidence).

Chemotherapy is indicated for patients with refractory and/or relapsed disease. Therapy as for MM is indicated (grade C recommendation, based on level IV evidence).

Other treatment approaches. There is no theoretical indication for, and no available data on, the use of bisphosphonates in SEP. Thalidomide has been used to treat extramedullary plasmacytoma in the context of relapsed MM with variable results (Biagi *et al*, 2001; Blade *et al*, 2001; Myers *et al*, 2001), but there is no published data on its use in SEP.

Patient information and support

Provision of appropriate patient information and support forms an important part of the care of patients with SBP and SEP. General principles are the same as those for patients with myeloma (UK Myeloma Forum, 2001). The International Myeloma Foundation (UK) produces a booklet for patients with solitary plasmacytoma.

Disclaimer

The advice and information in these guidelines is believed to be true and accurate at the time of going to press. However, the authors, the British Society for Haematology and the publishers do not accept any legal responsibility or liability for any errors or omissions that may have been made.

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