

RESEARCH ARTICLE

Radiotherapy Alone is Associated with Improved Outcomes Over Surgery in the Management of Solitary Plasmacytoma

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Abstract

Background: A moderate dose of radiation is the recommended treatment for solitary plasmacytoma (SP), but there is controversy over the role of surgery. Our study aimed at comparing different treatment modalities in the management of SP. **Materials and Methods:** Data from 38 consecutive patients with solitary plasmacytoma, including 16 with bone plasmacytoma and 22 with extramedullary plasmacytoma, were retrospectively reviewed. 15 patients received radiotherapy alone; 11 received surgery alone, and 12 received both. The median radiation dose was 50Gy. All operations were performed as radical resections. Local progression-free survival (LPFS), multiple myeloma-free survival (MMFS), progression-free survival (PFS) and overall survival (OS) were calculated and outcomes of different therapies were compared. **Results:** The median follow-up time was 55 months. 5-year LPFS, MMFS, PFS and OS were 87.0%, 80.9%, 69.8% and 87.4%, respectively. Univariate analysis revealed, compared with surgery alone, radiotherapy alone was associated with significantly higher 5-year LPFS (100% vs 69.3%, $p=0.016$), MMFS (100% vs 51.4%, $p=0.006$), PFS (100% vs 33.7%, $p=0.0004$) and OS (100% vs 70%, $p=0.041$). **Conclusions:** Radiotherapy alone can be considered as a more effective treatment for SP over surgery. Whether a combination of radiotherapy and surgery improves outcomes requires further study.

Keywords: Solitary plasmacytoma - radiotherapy - prognostic factors - multiple myeloma

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Introduction

Solitary plasmacytoma (SP), accounting for 5% to 10% of all plasma cell neoplasms (Dimopoulos et al., 2002; Ozsahin et al., 2006), is a rare malignancy defined as a proliferation of monoclonal plasma cells without any systematic involvement. Two subsets are categorized in terms of the location--solitary plasmacytoma of bone (SBP) and extramedullary plasmacytoma (EMP). SBP usually locates in the axial skeleton while EMP occurs in soft tissues, mainly in the head and neck area (Dimopoulos et al., 2002). SP responds well to local treatment. 10-year local control rate reaches to 81-95% (Chak et al., 1987; Tsang et al., 2001; Reed et al., 2011; Sasaki et al., 2012; Suh et al., 2012). Median survival time is reported to be 7-12 years (Knowling et al., 1983; Chak et al., 1987; Frassica et al., 1989; Liebross et al., 1998; Bachar et al., 2008). However, in spite of a curative treatment, some cases progress to multiple myeloma (MM) eventually, approximately 60% in SBP (Bataille et al., 1981; Ozsahin et al., 2006; Reed et al., 2011) and 8-64% in EMP (Strojan et al., 2002; Ozsahin et al., 2006; Bachar et al., 2008; Reed et al., 2011; Suh et al., 2012). Once the disease

becomes systemic, the prognosis is similar to patients initially diagnosed with MM, and 5-year OS decreases to 33% (Mendenhall et al., 1980). Therefore, it is of great importance to distinguish patients on risk of recurrence, and define effective primary therapy to prevent local relapse and MM development.

To our knowledge, radiotherapy (RT) with curative intent is widely accepted, yielding a satisfactory local control rate. Both guidelines from the National Comprehensive Cancer Network (NCCN, version 4, 2014) and British Society for Haematology placed RT as a priority for SP (Soutar et al., 2004). Nevertheless, whether surgery plays a beneficial role is still controversial although there is a consensus on surgical intervention in the management of pathological fracture, release of neurological symptoms and surgical biopsy in SBP (Sundaresan et al., 1994; Soutar et al., 2004). Some researchers demonstrated that the addition of surgery contributes to enhancing local control and disease-free survival (DFS) as well (Ozsahin et al., 2006; Kilciksiz et al., 2008). However, in EMP, the effect of surgery is disputed. NCCN guideline recommends RT alone, surgery alone or combination of RT and surgery, while

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the British Society for Haematology guideline considers surgery of the head and neck area inappropriate since the complexity of anatomy. Up to now, whether surgery can benefit patients with SP remains unclear. Our study aimed at identifying the different therapies with various clinical outcomes.

Materials and Methods

Subjects

From 1996 to 2013, data of 38 consecutive patients diagnosed as solitary plasmacytoma and treated in Sun Yat-Sen University Cancer Center were retrospectively analyzed. All patients were under complete examination and met the following criteria: (i) a solitary biopsy-confirmed lesion of neoplastic plasma cells; (ii) no clinical or radiographic evidence of any extra site of disease; evaluated by either a complete skeletal survey or bone scan were reviewed for the evaluation; (iii) bone marrow biopsy showed less than 10% plasma cells; (iv) absence of hypercalcemia, significant cytopenia, renal dysfunction, elevated immunoglobulin levels, abnormal serum protein electrophoresis, or urine protein electrophoresis. After treatment, patients were followed up and regularly reevaluated by clinical assessment and imaging.

The study was performed in compliance with Declaration of Helsinki and was approved by ethics committee.

Statistical analysis

Endpoints of interest were local progression-free survival (LPFS), multiple myeloma-free survival (MMFS), progression-free survival (PFS) and overall survival (OS). Time was calculated from the date of pathologic diagnosis to the event of interest, which was local progression for LPFS, development to MM for MMFS, death or first disease progression for PFS, and death (from any cause) for OS. The Kaplan-Meier method was used to estimate the survival and recurrence curves. For each end point, detection of statistical differences between selected factors was achieved by the log-rank test. Statistics was conducted by SPSS 18.0. *p* value<0.05 was considered statistically significant.

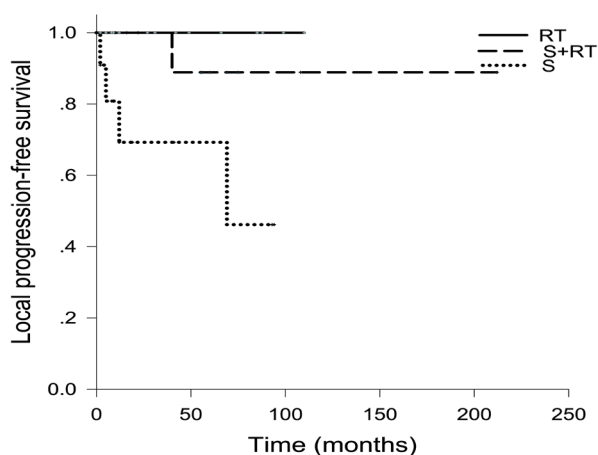


Figure 1. Local Progression-free Survival in 38 Patients with Different Treatment Modalities (*p*=0.014). RT: radiotherapy, S: surgery

Results

Patient characteristics

Characteristics of patients are detailed in Table 1. The median age at diagnosis was 48, 42 in SBP and 53 in EMP. 26 Patients were male, and 12 were female. The number of cases of SBP and EMP was 16 and 22, respectively. The most common presentation of SBP was found in the axial skeleton (10/16), while EMP occurred most frequently in the head and neck area (17/22). 9 patients were diagnosed with tumor >5cm. 15 patients in the study received definitive RT alone. 12 received surgery followed by definitive RT. 11 received surgery alone. Operations were all performed as radical resections. The median radiation dose was 50Gy.

Local control

The median follow-up time was 55 (range: 2-212) months. Complete remission was achieved in all patients after primary treatments. 5 patients had locally progressive disease. 5-year LPFS was 87.0%. The median time from diagnosis to local progression was 12 (range:2-59) months. Among these patients, 4 had single local relapse, and 1 patient finally developed MM. According to the univariate analyses, surgery (S) alone is an unfavorable factor of local control compared with RT alone (5-year LPFS: RT vs S+RT vs S: 100% vs 88.9% vs 69.3%, *p*=0.014, Figure 1. RT vs S: *p*=0.016; RT vs S+RT: *p*=0.35; S+RT vs S: *p*=0.063). In 16 patients with SBP, 5-year LPFS of RT vs S+RT vs S was 100% vs 88.9% vs 100% (*p*=0.76). In 22 patients with EMP, 5-year LPFS was 100% vs 100% vs 61.0% (*p*=0.029, RT vs S: *p*=0.012; RT vs S+RT: *p*=1; S+RT vs S: *p*=0.4).

Table 1. Patient Characteristics

Characteristics	Total.		SBP		EMP	
	No.	%	No.	%	No.	%
Age						
≥50	18	47.4	6	37.5	12	54.5
<50	20	52.6	10	62.5	10	45.5
Sex						
Male	26	68.4	12	75	14	63.6
Female	12	31.6	4	25	8	36.4
Subtype and location						
SBP	16	42.1				
Axial bone	10	62.5				
Others	6	37.5				
EMP	22	57.9				
Head and neck	17	77.3				
Others	5	22.7				
Tumor size						
≥5cm	9	23.7	8	50	1	4.5
<5cm	29	76.3	8	50	21	95.5
Radiotherapy/surgery						
RT alone	15	39.5	4	25	11	50
surgery alone	11	28.9	2	12.5	9	40.9
surgery+ RT	12	31.6	10	62.5	2	9.1
Radiation dose						
≥45Gy	18	66.7	8	57.1	10	76.9
<45Gy	9	33.3	6	42.9	3	23.1

SBP: solitary plasmacytoma of bone, EMP: extramedullary plasmacytoma, RT: radiotherapy

Table 2. Univariate Analyses of Prognostic Factors

Variable	n	5-y OS (%)	p	5-y PFS (%)	p	5-y LPFS (%)	p	5-y MMFS (%)	p
All patients	38	87.4		69.8		87		80.9	
Age									
≥50	18	81.7	0.25	56.3	0.067	86.9	0.55	65.5	0.038
<50	20	91.7		81.6		87.1		94.7	
Gender									
Male	26	85.9	0.79	64.5	0.74	85.3	0.63	76.7	0.77
Female	12	90.0		82.5		91.7		90.0	
Subtype									
SBP	16	84.4	0.42	64.5	0.65	92.9	0.16	70.0	0.13
EMP	22	94.4		79.5		84.2		94.4	
Tumor size									
≥5cm	9	100	0.15	77.8	0.60	87.5	0.56	88.9	0.78
<5cm	29	80.9		65.3		88.2		74.4	
Treatment									
Surgery+RT	12	87.5	0.049	71.3	0.001	88.9	0.014	80.2	0.035
RT alone	15	100		100		100		100	
Surgery	11	70.0		33.7		69.3		51.4	

SBP: solitary plasmacytoma of bone, EMP: extramedullary plasmacytoma, OS: overall survival, PFS: progression-free survival, LPFS: local progression-free survival, MMFS: multiple myeloma-free survival, RT: radiotherapy

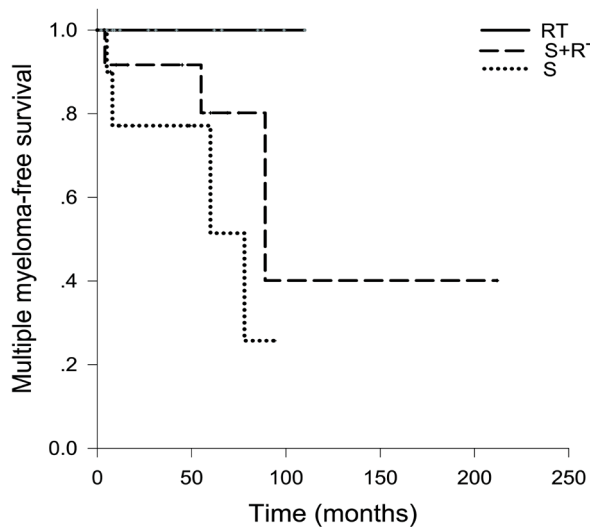


Figure 2. Multiple Myeloma-free Survival in 38 Patients with Different Treatment Modalities ($p=0.035$). RT: radiotherapy, S: surgery

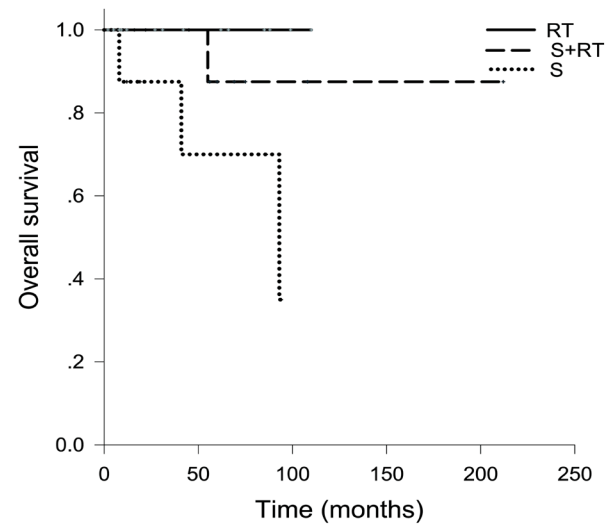


Figure 4. Overall Survival in 38 Patients with Different Treatment Modalities ($p=0.049$). RT: radiotherapy, S: surgery

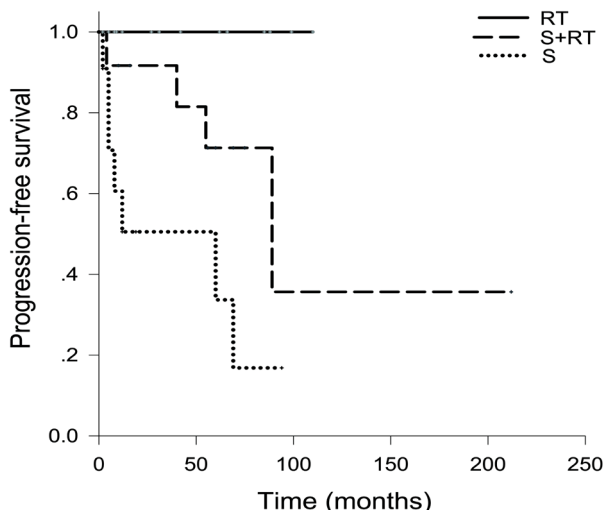


Figure 3. Progression-Free Survival in 38 Patients with Different Treatment Modalities ($p=0.0012$). RT: radiotherapy, S: surgery

Progression to MM

Progression to MM was observed in 7 patients. The 5-year MMFS was 80.9%. Median time from diagnosis to MM occurrence was 55 (range: 4-89) months. Among

these patients, 6 had MM only, and 1 occurred with local progression. 4 patients with MM died of the disease. On univariate analyses, favorable factors for better MMFS were RT (5-year MMFS: RT vs S+RT vs S: 100% vs 80.2% vs 51.4%, $p=0.035$, Figure 2. RT vs S: $p=0.006$; RT vs S+RT: $p=0.082$; S+RT vs S: $p=0.33$) and age<50 (5-year MMFS: 94.7% vs 65.5%, $p=0.038$). In 16 patients with SBP, 5-year MMFS was 100% vs 88.9% vs 100% ($p=0.053$). In 22 patients with EMP, 5-year MMFS was 100% vs 100% vs 83.3% ($p=0.14$).

Progression-free survival and Overall survival

Overall progression was noted in 11 patients. A total of 4 patients had died. The 5-year PFS and 5-year OS were: 69.8% and 87.4%. Univariate analyses identified RT as a favorable prognostic factor for 5-year PFS (RT vs S+RT vs S: 100% vs 71.3% vs 33.7%, $p=0.001$, Figure 3; RT vs S: $p=0.0004$; RT vs S+RT: $p=0.048$; S+RT vs S: $p=0.06$) and 5-year OS (RT vs S+RT vs S: 100% vs 87.5% vs 70.0%, $p=0.049$, Figure 4; RT vs S: $p=0.041$; RT vs S+RT: $p=0.35$; S+RT vs S: $p=0.13$). In 16 patients with SBP, 5-year PFS was 100% vs 70.0% vs 0% ($p=0.087$). 5-year OS was 100% vs 87.5% vs 50.0% ($p=0.083$). In 22 patients with EMP, 5-year PFS was 100% vs 100% vs

50.8%, ($p=0.011$, RT vs S: $p=0.005$; RT vs S+RT: $p=1$; S+RT vs S: $p=0.31$). 5-year OS was 100% vs 100% vs 83.3% ($p=0.37$).

Univariate analyses of prognostic factors is summarized in Table 2.

Discussion

Solitary plasmacytoma is an uncommon form of plasma cell neoplasms. Due to its rarity, most of our knowledge derives from retrospective studies, which usually regard RT as the most effective therapy. After a moderate (40-50Gy) dose of radiation (Mendenhall et al., 1980; Mendenhall et al., 2003; Kilciksiz et al., 2008), a 5-year local control rate of 81-95% could be expected (Ozsahin et al., 2006; Sasaki et al., 2012; Suh et al., 2012). 5-year overall survival rate is reported to be 70-78% (Frassica et al., 1989; Reed et al., 2011; Suh et al., 2012). 5-year MMFS ranges from 47 to 52% (Reed et al., 2011; Suh et al., 2012) and 5-year PFS from 43 to 56% (Frassica et al., 1989; Sasaki et al., 2012; Suh et al., 2012). Similarly, in the current study, though various treatments were used, 5-year LPFS, MMFS, PFS and OS are 87.4%, 69.8%, 87.0% and 80.9%, respectively, comparable to previous studies. When investigating clinicopathological characteristics, age<50 was a favorable predictive factor of MM development, which is in agreement with the former researchers (Khan et al., 2006; Kocak et al., 2010).

The role of surgery remains controversial in the management of SP. There are only a few reports on surgery alone in SP since the satisfactory local control following RT. Results of surgery alone were not optimal, carrying high rates of local recurrence (78%) (Ozsahin et al., 2006). Bacher et al. studied 68 patients with head and neck EMP undergoing various treatments (Bachar et al., 2008). To their opinions, although not statistically significant, there was a trend towards increased local control rate in patients treated primarily with radiation than those treated with other modalities, e.g. surgery+RT or chemotherapy. However, according to Strojan et al., no difference on outcomes was found between 15 patients receiving surgery+RT and 12 patients receiving RT alone. As they considered, close observation is preferred rather than adjuvant RT after R0 resection (Strojan et al., 2002). Interestingly, a research including 57 SBPs and 23 EMPs showed surgery+RT resulted in significantly longer PFS, compared with RT alone (median PFS 7.4 years vs 2.6 years) (Kilciksiz et al., 2008). But this conclusion should be interpreted in caution because EMP, which has a better prognosis intrinsically, is usually associated with a higher portion of excisional biopsy due to its derivation from soft tissue. In our study, RT alone is related to a significantly superior 5-year LPFS, MMFS, PFS and OS compared with surgery alone, supporting RT alone as a primary choice. The delay of definitive RT by the first consideration of surgery may be regarded as an important weakness of surgery+RT strategy.

SBP and EMP represent subgroups of different nature. Additionally, head & neck and non- head & neck EMP response to treatment differently. As mentioned before, neither American nor British guideline agrees a routine

use of surgery in SBP. But for EMP there is a controversy. Thus, a more detailed analysis is in need. In several studies, patients with head & neck EMP were free of disease after surgery alone (Kotner et al., 1972; Batsakis et al., 1983). Alexiou et al. reviewed 714 cases (82.2%) with lesion found in the upper aerodigestive tract and other 155 (17.8%) found in other body regions. Patients with non-upper aerodigestive tumor had similar risk of recurrence no matter they received RT, surgery or combined treatments. But interestingly, for upper aerodigestive tract EMP, higher OS and RFS were detected in those received surgery+RT (Alexiou et al., 1999). More recently, Gerry et al. reported EMP in the head & neck area responded better to surgery than RT or surgery+RT (Gerry et al., 2013), while some researcher held a contrary opinion (Michalaki et al., 2003; Creach et al., 2009). To be noticed, it is not always possible to remove an EMP completely, especially in the head & neck area due to the adjacent vital organs structures, highlighting the importance of lesion location in treatment planning. Our study revealed, when SBP and EMP were analyzed independently, the power to detect significant difference was not enough because of the small sample number. But RT still showed its advantage in LPFS and PFS for EMP patients. Since the recommended RT dose for SP is not high, we suggest RT alone as a primary consideration when the toxicity is tolerable. A following resection may be saved for salvage therapy.

Another debate is whether patients on high risk benefit from chemotherapy, surgery+RT or higher RT dose. A previous research demonstrated tumor size>5cm as a risk factor for local recurrence. The authors believed RT combined with chemotherapy a possible way to improve outcome (Tsang et al., 2001). Some researchers declared local control was increased in head & neck EMP when dose>45Gy (Tournier-Rangard et al., 2006). However, Ozsahin et al. (2006) concluded, even for large tumors, higher RT dose failed to make any improvement above 30Gy. In our study, in 10 cases presented with tumor>5cm, only one received 36Gy resulted in local failure. Thus, we believe dose escalation is only potentially beneficial, requiring for evidence from well-designed studies. On the other hand, risk factors for MM are: serum $\beta 2$ microglobulin ≥ 3.5 mg/L (Guo et al., 2013), bone invasion (Ozsahin et al., 2006), involvement of axial bone (Bataille et al., 1981), age (Tournier-Rangard et al., 2006), monoclonal urinary light chains (Hill et al., 2014) and positive multiparameter flow cytometry (Paiva et al., 2014). Reported by Huang et al., in patients with SP of cervical spine, adjunctive RT following excision obviously decreased MM progression (Huang et al., 2010). Another retrospective study showed favorable effects related to melphalan-based chemotherapy in preventing MM development (Mayr et al., 1990), but others didn't report any benefits of chemotherapy (Holland et al., 1992; Katodritou et al., 2014). Unfortunately, our study doesn't have the potency to explore the effectiveness of intensive therapy in patients of high risk owing to the small number of events.

In conclusion, RT alone is primarily recommended for SP, while routine use of surgery alone should be avoided. The role of surgery+RT needs to be further studied.

Although some risk factors have been identified, there is not enough evidence supporting intensive treatment including surgery+RT or high dose RT. Prospective studies with larger sample size are expected to provide higher level of evidence.

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