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Patterns of Practice in Palliative Radiotherapy for Bone Metastases in UK centres

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Abstract

Background: There is abundant evidence of the comparative efficacy of single-fraction (SF) radiotherapy and multi-fraction (MF) radiotherapy when treating patients with bone metastases. Despite this, previous surveys have shown SF schedules to be underutilised.

Aim: To determine current patterns of practice in patients with bone metastasis and to investigate the factors that influence practice.

Method: An electronic audit was performed amongst 46 physicians, within 7 hospital trusts in the UK. The audit comprised of 4 hypothetical cases in which consultants and registrars choose which dose and fractionation they would recommend and their reasons for this recommendation.

Results: SF radiotherapy was the most common radiotherapy schedule in hypothetical cases 1, 3 and 4. SF radiotherapy was recommended by 65% of respondents in case 1, 47% in case 2, 89% in case 3 and 46% in case 4. For case 2, 50% proposed MF radiotherapy. For case 4, 22% of respondents recommended SABR. The following deciding factors were cited as influencing choice of a SF schedule: prognosis, published evidence, performance status and spinal cord compression.

Conclusion: The most common radiotherapy schedule selected was SF. However, there are inter-institution differences regarding the use of SF radiotherapy. Furthermore, the survey had shown that a third of respondents recommended a MF regime, despite evidence supporting the efficacy of a single fraction schedule.

Introduction

After lung and liver, the skeletal system is the most common location for metastasis⁽¹⁾. Skeletal metastases develop in 70-80% of patients with breast or prostate cancer and in up to 40% of patients with advanced stage lung cancer⁽²⁾.

Bone metastases can cause significant morbidity. The management of bone metastases depends upon location as well as patient performance status and previous treatment⁽¹⁾. Therapeutic options include: analgesics, systemic therapy, bisphosphonates and radiotherapy. The purpose of such treatments are to relieve pain and reduce risk of fractures. Treatments can also prevent problems linked with untreated progressive disease such as spinal cord compression⁽³⁾.

It has been found that 50% of cancer patients will have palliative radiotherapy during the course of their disease. Palliative radiotherapy has a 50-80% likelihood of overall pain relief⁽⁴⁾.

Randomised controlled trials have been carried out comparing single and multiple fractionated (SF and MF) regimes. Even though the findings have shown a comparative efficacy of both single and multiple fractionated schedules, it has been shown single fraction treatments remain underused^(5; 6; 7; 8;9).

The aim of this study is to carry out an audit of a number of radiotherapy departments and their current external beam radiotherapy regimes to investigate factors associated with the choice of dose and fractionation in the treatment of bone metastases.

Ethical Issues

Participants and their trusts were assured of their and their trusts anonymity and permission were granted from the managers at each department. Nine departments were contacted which had a partnership with Sheffield Hallam University.

With regards to approval of this study, the Faculty of Health and Wellbeing Research Ethics Committee was consulted, and approval received ⁽¹⁰⁾.

Once permission was gained, an email was sent to the consultants and registrars inviting them to take part.

Materials and Method:

An electronic audit was designed and performed amongst 46 physicians, within 7 hospital trusts. The 7 trusts used were partnered with Sheffield Hallam University as part of their 9 current training sites. This was distributed using Survey Monkey (Survey Monkey Solutions, Dublin, Ireland). An advantage of an electronic audit is that they tend to acquire a greater response compared to postal surveys ⁽¹¹⁾.

The audit comprised of open and closed questions, 4 hypothetical cases of patients with bone metastases as well as general demographic questions. Population, Exposure and Outcome (PEO) and Population, Intervention, Comparison, Outcome (PICO) research models were used to help shape and define questions.

The hypothetical cases used within the survey were adapted from previous studies to allow comparisons to be made ^(5; 6; 7;9). Table 1 describes the hypothetical cases that were used in the survey. See Appendix 1 which shows the full survey.

Case 1	A 55-year-old woman has metastatic
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	breast cancer with evidence of disease in the liver. The bone scan shows increased uptake of radionuclide at T6-T9. There is no evidence of spinal cord compression. Her ECOG performance status is 1.
Case 2	A 55-year-old woman has metastatic non-small cell lung cancer. Radiologic examinations showed osteolytic bone metastasis at L3. There is evidence of mild vertebral collapse, with spinal cord compression on magnetic resonance imaging scan. Her ECOG performance status is 1.
Case 3	A 70-year-old man has metastatic hormone-refractory prostate cancer. The bone scan shows an uptake within the left shoulder. On plain X-ray, there are osteoblastic lesions without pathological fractures in the left shoulder. His ECOG performance status is 1.
Case 4	A 68-year-old man has previously been treated for renal cancer with a nephrectomy. Two years later he presents with pain in his back in which the MRI scan shows a solitary metastasis on T12 with no evidence of spinal cord compression. His ECOG performance status is 2

Table 1: Hypothetical cases

Key: T= Thoracic; L= Lumbar; ECOG= Eastern Cooperative Oncology Group

A pilot study was carried out in one of the clinical sites to test the survey and determine whether further development to the questionnaire was needed. Minor changes were introduced as a result of the pilot ⁽¹²⁾.

Sampling

The sampling method that was used was voluntary convenience sampling.

Consultants and registrars in oncology were invited to participate via email.

Data analysis

The data was analysed using the Statistical Package for Social Sciences (SPSS), version 24. There was a mixture of qualitative and quantitative questions used. The type of variable used established how the data was presented⁽¹³⁾. Quantitative variables would include nominal or ordinal variables which can be presented using graphs to identify any patterns. In this case, the nominal variables were the number of consultants that prescribed a certain fraction for a hypothetical case.

The data was represented using bar graphs (see fig 1 and 2.) so that comparisons could be made⁽¹³⁾. In that, the radiation dose prescription that each consultant and registrar decided to prescribe were compared for each hypothetical case. The data was also presented in tables 2 and 3, so that cross-tabulation could occur.

As categorical data was produced a chi-square test (χ^2) performed to test significance between two variables such as factors associated with the choice in fractionation⁽¹⁴⁾. A P value lower than 0.05 was considered to indicate statistical significance.

Discussion and Results.

Single fraction vs. Multiple fractionated regime when treating bone metastases

Studies have compared the efficacy of a SF to MF schedules when treating patients with bone metastases. In terms of MF regimes, they have varied from: 20 Gy in 5 fractions, 24 Gy in 6 fractions, 30 Gy in 10 fractions and 40 Gy in 20 fractions. The single fraction usually consists of either 6 Gy or 8 Gy⁽¹⁾.

A systematic review and meta-analysis of the literature, which compared SF radiotherapy to a MF schedule for patients with bone metastases was completed by Sze et al.⁽⁸⁾ in which eleven trials involving 3435 patients were identified. The findings had shown that the overall pain relief response rate was 60% for patients that had a SF and 59% for those that had a MF regime of radiotherapy. Confidence intervals were 0.89 to 1 which infers that there were no differences in overall pain relief within the treatment schedules. The similarity between the treatment schedules regarding complete pain response implies that SF radiotherapy is as effective as multiple-fractionated radiotherapy, in terms of pain relief. Similar findings were shown by Arnalot et al.⁽¹⁵⁾, Chow et al.⁽¹⁶⁾ and Wu et al.⁽¹⁷⁾.

Strengths of a single fraction

Another advantage of SF treatments was demonstrated by Hartsell et al.⁽¹⁸⁾. Their results show that the SF schedule had less acute toxicity compared to the MF arm. This study only included patients with primary breast or prostate cancer which means outcomes may not be the same as other sites. However, Wu et al.⁽¹⁷⁾ compared factors such as pain relief and acute toxicities across different tumour types and found that there was no significant difference in pain relief. Furthermore, the quality of life assessment did not show a difference between the single and multiple fractionation arms.

Hartsell et al.⁽¹⁸⁾ further highlighted that SF radiotherapy offers a major economic advantage of savings in radiotherapy capacity. However, reimbursement and health infrastructure are different in the US than in the UK, making it difficult to apply these findings to the UK health care setting. Hartsell et al.⁽¹⁸⁾ stated that fewer visits to the hospital would result in lower cost for the patient.

Weaknesses of single fraction

One of the main drawbacks of delivering palliative radiotherapy in a SF is the retreatment rate being higher than a multiple fractionated regime. Chow et al. ⁽¹⁶⁾ found that the retreatment rate was 2.6-fold greater in the SF arm, statistically significant ($p=0.00001$). The reasoning behind this could be due to the radiation oncologists being more willing to retreat patients when they have had a SF due to SF treatments being well within the limits of radiation tolerance ^(17,19,20).

Another weakness of delivering the 8 Gy in a SF compared to MF schedule is the risk of a pathological fracture in the single fraction arm is greater ⁽¹⁶⁾. Though, the systematic review had shown that there was not a significant difference between the two when they had reviewed 10 trials that had reported pathological fracture rates. Despite the results not being statistically significant, there was a trend for lower rates in the multiple fractionation arm.

Stereotactic Body Radiotherapy

Stereotactic Body Radiotherapy (SABR) is a technique used to deliver a high dose of radiation to a target in a smaller number of fractions in comparison to conventional radiotherapy. This can provide better local control and longer symptom palliation in the setting of bone pain, compared to conventional radiation therapy. There are certain criteria that need to be met for SBRT treatment such as: well-circumscribed, inoperable lesion ⁽²¹⁾. Current published results suggest that we can use single-fraction at up to 20 Gy for relief of acute bone pain ⁽²¹⁾.

Studies to show patterns of practice

In spite of the number of randomised controlled trials showing the efficacy of delivering radiotherapy in a single fraction ^(8; 15; 16; 17), there is a variation in practice

on an international basis as well as differences between centres in the UK. For instance, a study distributed an electronic survey to radiation oncologists to find out their patterns of practice ⁽⁵⁾. The findings showed that the most prescribed schedule was 30 Gy in 10# emphasising a gap between evidence and practice. It also looked at the decision factors affecting dose prescription which allowed for comparisons to be made. In that, the oncologists were more likely to prescribe a shorter fractionation regime if the life expectancy of the patient was short.

As mentioned, patterns of practice may vary between radiotherapy centres. A review collated several trials to determine global patterns of practice ⁽²²⁾. It was found that radiation oncologists from the United States (US) and Asia were less likely to deliver radiotherapy in a single fraction (range: 1-15.6% of hypothetical cases) whereas patients in Canada, Australia and from the United Kingdom were more likely to receive a SF (range: 10.9–38.9%). The variation in practice may be due to: oncologist preference, possibly influenced by reimbursement, patient age and the number of sites of bone metastases ⁽²³⁾. It was concluded that a global reluctance still exists regarding the prescription of a single fraction of radiotherapy over the 20 years they had studied (1993-2013) ⁽²²⁾.

It was found that ⁽²⁴⁾, the utilisation rate of single-fraction was below 5% despite the American Society for Radiation Oncology (ASTRO) guidelines, as a result ASTRO published new guidance in 2017 ⁽²⁵⁾. This was due to new literature that had arisen since 2011 ⁽¹⁶⁾.

For this research an audit was undertaken and aimed to show what factors influenced the consultants in the UK with the choice of prescribed dose and differences between centres in the UK.

Aim/research question

“An audit of current external beam radiotherapy regimes in parts of the UK to investigate factors associated with the choice of dose and fractionation in the treatment of bone metastases.”

The literature review showed that there is a variation in patterns of practice when treating bone metastases despite there being abundant evidence and guidelines of the equivalence of SF to a MF regime. There are multiple factors that influence the choice of fractionation as discussed in the literature review. The recent publication by ASTRO ⁽²⁵⁾ could influence patterns of practice and standardise the care of patients with bone metastases.

A total of 46 clinical radiation oncologists returned responses. Seven out of the nine departments that work in partnership with Sheffield Hallam University took part in the audit. The distribution of the departments in the population of responders is shown in Figure 1. Of those responders, 39 were consultants and 7 were registrars.

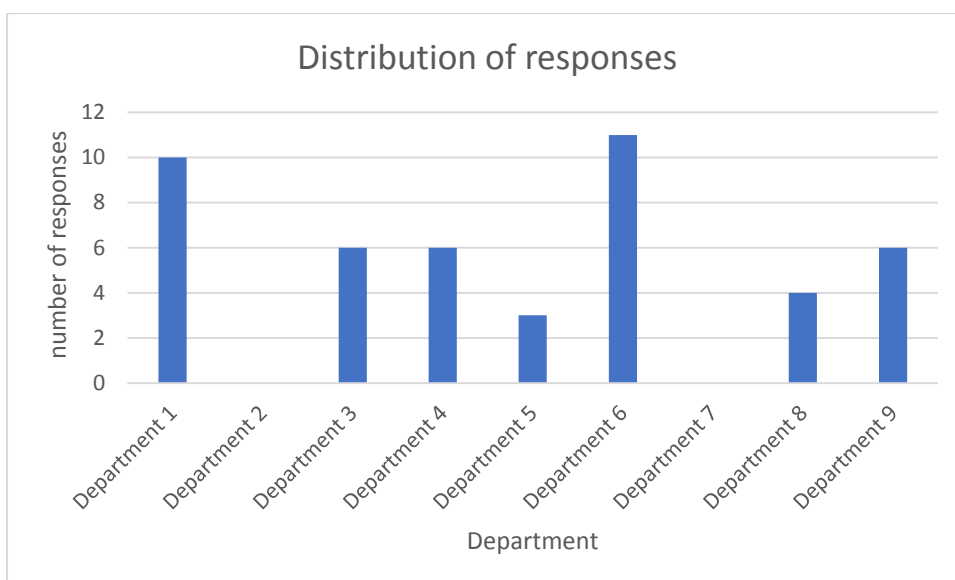


Figure 1: Distribution of responses

Fractionation for bone metastases

The recommended doses for cases 1 through to 4 are summarised in Figure 2. For case 1 and 3 the most commonly prescribed regimen was 8 Gy in 1#. Case 2 described a patient with mild vertebral collapse with evidence of spinal cord compression. The results show that 47.83% of respondents would deliver radiotherapy in a single fraction. For oligometastasis (case 4), 22% of respondents would prescribe a high-dose multi-fraction radiotherapy.

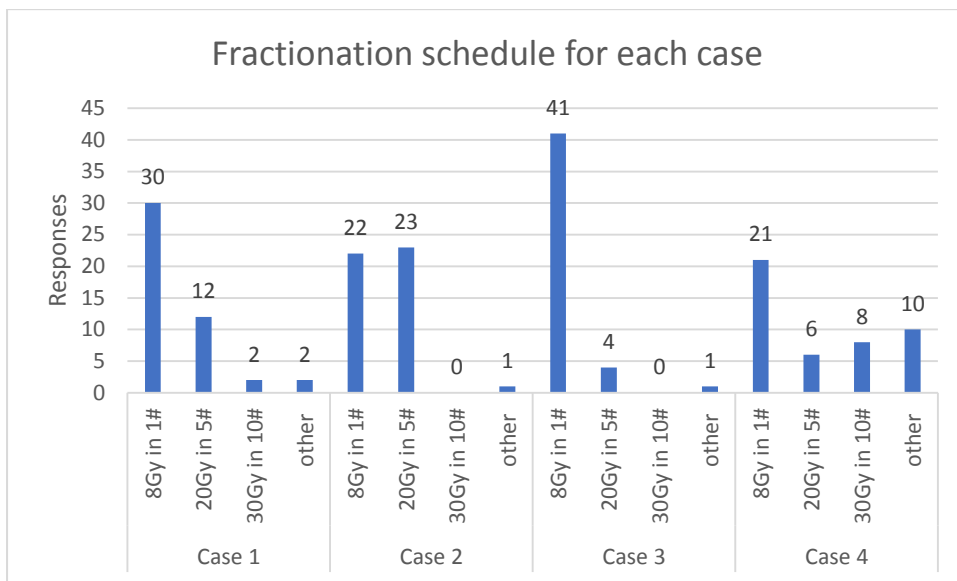


Figure 2: Fractionation schedule for each case

Factors associated with the fractionation schedule used

The results of the chi squared test had shown certain factors to have an influence on the fractionation schedule. Table 2 shows the factors that had a significant relationship between the single fraction and the factors for each case.

	Performance status	Published evidence	Prognosis	Site of metastasis	Spinal cord-compression
Case 1	1, N=46) = 18.87, p= .001	x2 (1, N=46) = 17.49, p= .001	(1, N=46) = 9.58, p= .002)	-	-
Case 2	-	(1, N=46) = 3.994, p= .046)	-	(1, N=46) = 3.994, p= .046)	(1, N=46) = 22.501, p= .001
Case 3	1, N=46) = 5.056, p= .025)	-	-	-	-

Case 4	-	(1, N=46) = 3.673, p= .05)	(1, N=46) = 4.862, p= .027)	(1, N=46) = 4.018, p= .045)	-
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Table 2: Significant factors influencing the decision of a single fraction

Inter-institution Differences

The results had shown that certain departments are more likely to choose a single fraction. Table 3 shows how many physicians at each department decided to prescribe 8 Gy in 1# for case 1. The physicians from department 9, all decided they would give a single fraction. Whereas, 66% of physicians at department 1 would choose the single fraction. Furthermore, the physicians at department 6 were more likely to choose a multi-fraction regime.

For case 2, table 3, shows that, all of the physicians at department 1 would prescribe 20 Gy in 5#. In comparison to this, all the physicians at department 4 and 5 would deliver radiotherapy in a single fraction. However, department 3,8 and 9 indicated differences within their departments.

Statistics Count		What department do you work in?						
		Department 1	Department 3	Department 4	Department 5	Department 6	Department 8	Department 9
8Gy in 1# for case 1	Yes	4	4	5	2	5	4	6
	no	6	2	1	1	6	0	0
Total		10	6	6	3	11	4	6
8Gy in 1# for case 2	Yes	0	3	6	3	7	1	2
	no	10	3	0	0	4	3	4
Total		10	6	6	3	11	4	6
8Gy in 1# for case 3	Yes	7	5	6	3	10	4	6
	no	3	1	0	0	1	0	0
Total		10	6	6	3	11	4	6
8Gy in 1# for case 4	Yes	1	4	1	2	8	1	4
	no	9	2	4	1	3	3	2
Total		10	6	5	3	11	4	6

Table 3: Comparison of departments for cases 1,2,3 and 4 recommending 8 Gy in 1#

Findings

This survey was performed to demonstrate patterns of practice in patients with bone metastases and to determine the factors affecting radiotherapy prescriptions. The

most commonly prescribed prescription was 8 Gy in 1#. However, multi fraction schedules are still being used. The factors influencing such decisions included: performance status, published evidence and site of metastasis. This varied depending on the hypothetical case. The factors least influencing such decisions were: department policy, finance, patient choice and patient age.

Case 1

The results had shown that the majority of consultants and registrars would use a SF (65.2%). This case was modified from a study, ⁽⁶⁾ to allow comparisons to be made. In fact, their results had shown that only 12.1% of all respondents recommended SF radiotherapy. This suggests that since 2009, an increased uptake in consultants preferred to use SF radiotherapy.

Furthermore, there was a significant relationship between the use of 8 Gy in 1# and the influence of published evidence, $\chi^2 (1, N=46) = 17.49, p = .001$. Having said that, there was also a significant relationship between 20 Gy in 5# and the influence of published evidence, $\chi^2 (1, N=46) = 11.576, P = .001$.

There was a significant relationship between SF radiotherapy and prognosis, $\chi^2 (1, N=46) = 9.58, p = .002$. This is comparable to other studies such as: ⁽⁵⁾ who found that 69.3% of respondents felt that the prognoses of patients are a factor that would influence their decision. It was found that 46% of respondents would choose SF radiotherapy if the patient has a poor prognosis ⁽³⁾. A study ⁽⁶⁾ stated that stated that due to the limited survival of palliative patients, the use of SF radiotherapy is recommended, to decrease the time spent in medical appointments

Case 1 involved disease at T6-T9. It is not feasible to use SABR to treat extensive multilevel disease that involves the spine ⁽²¹⁾. However, a respondent recommended a “SBRT type dose if she has oligometastatic disease”.

Another respondent stated that, travelling distance can be a factor, but “other factors selected usually have more of an impact on choice of dose/fractionation”. As part of the reasoning from Lutz et al. ⁽²⁵⁾ recommending the use of a SF, it was mentioned that a single 8 Gy fraction provides a none inferior pain relief compared to a MF regime, which can be convenient for patients with a poor prognosis. Patient convenience was an important factor when recommending the fractionation, in 3.4% of patients ⁽⁵⁾. This indicates that this is not one of the main factors in determining dose ⁽⁵⁾.

Case 2

For case 2, 22 respondents (47.83%) selected delivering a SF schedule whereas, 24 respondents (52.17%) chose a multi-fractionated regime. Indicating differences in the dose prescription when patients have spinal cord compression. A comparable case about spinal cord compression was in a survey distributed in Italy ⁽⁹⁾. The results had shown that 30% of respondents would prescribe SF radiotherapy. The low use of SF radiotherapy was attributed to the perceived risk of cord compression and that neuropathic pain requires high doses to alleviate pressure on nerves. Nakamura et al. ⁽⁷⁾ included a comparable case within their study and the findings had shown that 79% of respondents would deliver using a multi-fractionated regime. However, a small sample size reduces reliability in this study.

On the other hand, two respondents noted that “SCORAD trial results” influenced their decision of choosing a SF. Hoskin et al. ⁽²⁶⁾ compared 8 Gy in 1# to multiple fractions for patients with spinal-cord compression and found that using a single

dose of 8 Gy is as effective in terms of overall survival. Therefore, it is recommended to use a single dose in this setting, with the main benefit of requiring a single visit.

In terms of the factors influencing the respondent to choose a SF, there was a significant relationship between spinal cord compression and delivering a single fraction, $\chi^2 (1, N=46) = 22.501, p = .001$. Also, there was a significant relationship between published evidence and delivering a single fraction, $\chi^2 (1, N=46) = 3.994, p = .046$.

Case 3

Case 3 described a hormone-refractory prostate cancer patient, who presented with progression of pain which was found to be osteoblastic lesions in the left shoulder. The findings had shown that 89.3% of respondents would choose SF radiotherapy. The survey distributed by Fairchild et al. ⁽⁶⁾ had a comparable case which was also found to have 8 Gy in 1# as the most common regimen. There was a significant relationship between prognosis and delivering a SF as $p=0.01$. This is because of the limited survival of patients and the importance of decreasing the time invested in hospital appointments ⁽⁶⁾.

A respondent chose to deliver a SF schedule but stated the increased likelihood of retreatment due to this. As mentioned, Chow et al. ⁽¹⁶⁾ found that the retreatment rate was 2.6-fold greater in the SF arm compared to MF. However, this could be due the radiation oncologists being more willing to retreat patients as the sum of both treatments would be within the limits of radiation tolerance ⁽¹⁷⁾.

Case 4

Finally, case 4 describes a patient with a solitary metastasis on T12 who had previously been treated for renal cancer. Twenty-one (46.67%) respondents chose

SF radiotherapy. There was a significant relationship between 8 Gy in 1# and poorer prognosis compared to MF regimes $\chi^2 (1, N=46) = 4.862, p= .027$. Therefore, consultants are more likely to prescribe 8 Gy in 1# as a result of prognosis. Again, published evidence was a significant factor influencing respondents to choose SF radiotherapy, $\chi^2 (1, N=46) = 3.673, p= .05$.

In terms of multi-fraction radiotherapy, 14 respondents (30%) recommended this. In that, 8 respondents chose 30 Gy in 10# and 6 respondents chose 20 Gy in 5#.

However, ten (22.22%) respondents suggested a SABR dose due to it being a solitary metastasis. Nakamura et al. ⁽⁷⁾ had a comparable case about oligometastasis, in which 15/52 (29%) respondents recommended a high dose. Jhaveri et al. ⁽²¹⁾ looked at SABR for bone metastases to investigate the impact of high doses at a target using single or multiple doses. It was found that SBRT can be safe and effective in relieving bone pain from metastatic disease. Current published results have shown that SF-SBRT of up to 20 Gy can be used to relieve bone pain ⁽²¹⁾. One of the respondents suggested a dose of 20Gy in 5# and mentioned that it is a resistant disease. However, Jhaveri et al. ⁽²¹⁾ stated that doses of up to 20Gy can also be used for radioresistant tumour types such as renal cell carcinoma. The implications of this is that, in the future the use of SABR may increase due to the positive findings studies have shown.

Inter-institution differences

As mentioned, certain departments are more likely to deliver SF radiotherapy such as departments 4, 5 and 6 (see table 3).

In terms of the frequency of respondents of each departments suggesting SABR for case 4 in a SF, there were 4, 3,2,1 number of respondents from department 1,4,8

and 3 respectively. This could be due to the increased use of SABR within these departments.

Limitations

Limitations include the primary researchers lack of experience in this type of research.

Another limitation was the small sample size. Due to the small absolute sample size (n = 46), the results might not accurately represent the practice of physicians in the UK. Previous studies regarding patterns of practice with patients that have bone metastases have stated the response rate of the health professionals involved in their studies have been low which can affect the validity and reliability of their findings. Magne et al. ⁽³⁾ had a response rate of 15.7% and Nakamura et al.'s ⁽⁷⁾ study had a response rate of 36%.

Conclusion

This survey has shown that the results tally with recent guideline recommendations ⁽²⁵⁾. In that, the majority of respondents recommended a SF to treat patients with bone metastases. The factors which had influenced the consultants and registrars to choose a SF schedule were: published evidence, prognosis, performance status and spinal cord-compression. The factors considered the least often were: patient choice, finance, late side effects and department protocol. But, about a third of respondents indicated use of MF regimes. The use of SABR may increase in the future due to studies supporting the its use in a palliative setting for patients with solitary metastases.

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Conflicts of Interest

None.

Ethical Standards

This research did not include any human or animal experimentation

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Appendix 1

1) What department do you work in?

N.B The question allows data to be collated for analysis but the name of the centre will be anonymised when the findings are being carried out

Case 1:

A 55-year-old woman has metastatic breast cancer with evidence of disease in the liver. The bone scan shows increased uptake of radionuclide at T6-T9. There is no evidence of spinal cord compression. Her ECOG performance status is 1. Abbreviation: ECOG = Eastern Cooperative Oncology Group. Assume that you decide to give external beam radiotherapy, what dose and fractionation would you give?

Assume that you decide to give external beam radiotherapy, what dose and fractionation would you give?

- 8Gy in 1#
- 20Gy in 5#
- 30Gy in 10#
- Other dose. Please specify: _____

Please tick all boxes that would influence your choice of dose and fractionation, for this case and similar cases.

- Performance status
 - Site of metastasis
 - Patient age
 - Patient choice
 - Financial aspects
 - Published evidence.
 - Late Side effects
 - Spinal cord compression (present or impending)
 - Prognosis
 - Departmental protocol
- Other. Please specify: _____

Case 2:

A 55-year-old woman has metastatic non-small cell lung cancer. Radiologic examinations showed osteolytic bone metastasis at L3. There is evidence of mild vertebral collapse, with spinal cord compression on magnetic resonance imaging scan. Her ECOG performance status is 1. Assume that you decide to give external beam radiotherapy, what dose and fractionation would you give?

Same layout as case 1

Case 3:

A 70-year-old man has metastatic hormone-refractory prostate cancer. The bone scan shows an uptake within the left shoulder. On plain X-ray, there are osteoblastic lesions without pathological fractures in the left shoulder. His ECOG performance status is 1. Assume that you decide to give external beam radiotherapy, what dose and fractionation would you give?

Same layout as case 1

Case 4:

A 68-year-old man has previously been treated for renal cancer with a nephrectomy. Two years later he presents with pain in his back in which the MRI scan shows a solitary metastasis on T12 with no evidence of spinal cord compression. His ECOG performance status is 2. Assume that you decide to give external beam radiotherapy, what dose and fractionation would you give?

Same layout as case 1

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

T= Thoracic

L= Lumbar