Stereotactic ablative body radiotherapy for prostate cancer

Questions to be addressed

1. What is the clinical effectiveness of stereotactic ablative body radiotherapy for prostate cancer which is considered not suitable for surgery (because of medical co-morbidity or because lesion is inoperable), compared to best standard care?

2. What is the cost effectiveness of stereotactic ablative body radiotherapy for prostate cancer which is considered not suitable for surgery (because of medical co-morbidity or because lesion is inoperable), compared to best standard care?

Summary

Background

- Stereotactic ablative body radiotherapy (SABR) is a targeted mode of radiation therapy. It can be used to treat carcinoma of the prostate, but there is uncertainty about the clinical and cost effectiveness of this approach.

Clinical effectiveness

- We found no randomised controlled trials.
- We found one systematic review:
    - The authors found no controlled trials of the effectiveness of SABR for prostate cancer.
    - They included 14 uncontrolled studies which reported a total of 1472 participants. Biochemical progression-free survival was more than 81% in all the studies, after median follow-up of 11 to 60 months.
    - The systematic review reported that the commonest form of acute toxicity was urinary, with grade 1 (least severe) adverse effects reported in 20% to 74% of participants. Grade 1 acute rectal toxicity occurred in 3% to 75% of participants.
    - The review included four studies reporting quality of life, three uncontrolled and one controlled. Of the three which were uncontrolled, two reported that quality of life declined in the first few months after SABR but then returned to baseline levels, and one reported no overall changes.
    - The fourth study compared radical prostatectomy with SABR. It reported that the men who had SABR had smaller and briefer declines in quality of life related to urinary symptoms, and avoided the loss of sexual quality of life that followed prostatectomy. There was a larger and more prolonged decline in bowel quality of life after SABR than after surgery. This study is unreliable because of marked confounding between the two groups.

- We found one controlled study reporting oncological outcomes published since the search date of the systematic review. It compared SABR with or without external beam radiotherapy in men with high-risk non-metastatic prostate carcinoma, and reported that five-year biochemical disease-free survival was 68% overall, which was similar in the two groups. However, these results are of doubtful validity.
- We found thirteen uncontrolled studies not included in the systematic review. We excluded studies with fewer than a hundred participants; including these small uncontrolled studies would have not provided any further information on the effectiveness of SABR relative to other treatments.
- This left one study, which reported seven-year biochemical disease-free survival of 94% and overall survival of 85%.
- A safety study published since the systematic review indicates that SABR leads to more genito-urinary and gastro-intestinal adverse effects than intensity-modulated radiotherapy (IMRT).

Cost effectiveness

- We found three analyses from the United States which concluded that the lower costs of SABR lead to better apparent cost effectiveness than IMRT. However, the analyses have a number of limitations which restrict their relevance and reliability.

Activity and cost

- No cost or activity data were available.

Equity issues

- We identified no specific equity issues.

1 Context

1.1 Introduction

Stereotactic ablative body radiotherapy (SABR) is a targeted mode of radiation therapy. It can be used to treat prostate cancer, but there is uncertainty about the clinical and cost effectiveness of this approach.

1.2 Existing national policies and guidance

We found no national policies or guidance based on systematic reviews of the evidence. SABR is not mentioned in NICE's guidance on the management of prostate cancer.

2 Epidemiology

Prostate cancer is the commonest cancer among British males. It affects about one in twelve men over a lifetime, giving rise each year to about 30,000 new cases and 10,000 deaths. Prostate cancer is particularly common among older men; two-thirds of those who die from prostate cancer are over the age of 75 years. Prostate cancer may be diagnosed when men are investigated for benign prostate disease, also a common condition in elderly men.

The disease varies widely in its clinical course, tending to be more aggressive in younger men. Sometimes prostate cancers grow so slowly that they pose no threat to health or longevity – autopsies in men over eighty years of age show that most have malignant tissue in their prostate glands, but they died with prostate cancer, not of it. Survival rates are better than for many other cancers.

External beam radiotherapy is widely used to treat prostate cancer. Compared with external beam radiotherapy, SABR offers the potential advantages of delivering a higher dose to the tumour with less collateral damage to normal tissue, and of requiring fewer fractions.

3 The intervention

Stereotactic ablative body radiotherapy (SABR) is a targeted mode of radiation therapy. It involves the use of radiation delivered from numerous angles so that only a small volume of tissue is exposed to the full dose. It can be delivered either as a single dose or in up to five fractions. It is an alternative to surgery or other forms of radiotherapy, especially in patients who cannot undergo surgery and for tumours that are hard to reach, located close to vital structures or subject to movement within the body.

4 Findings

In March 2015, we searched for evidence about the clinical and cost effectiveness of SABR for the treatment of prostate cancer. The question for this review concerned only men unsuitable for surgery, but we found few studies which applied this inclusion criterion. We have therefore included other studies to provide a more comprehensive report.

The search strategy is in the Appendix.

4.1 Evidence of effectiveness

We found no randomised controlled trials.

We found one systematic review:

- Tan et al reviewed studies of the effectiveness of SABR for prostate cancer (search date January 2014).[1] They excluded studies with fewer than ten participants or less than six months' median follow-up. They only included studies in which SABR was the sole form of radiotherapy used, in order to avoid the confounding effects of other radiation treatment. When an institution had several publications, only the most relevant was used, with care taken to prevent the inclusion of overlapping cohorts. All the participants were newly diagnosed and apparently without metastases.

  Tan et al found no controlled studies reporting oncological outcomes. They included 14 uncontrolled studies which reported a total of 1472 participants. Ten of the studies specified the use of androgen deprivation therapy, which may have influenced the outcomes independently of SABR. Tan et al did not meta-analyse their results, but reported that biochemical progression-free survival was more than 81% in all the studies, after median follow-up ranging from 11 to 60 months.

  Tan et al included four studies reporting quality of life, three uncontrolled and one controlled:

  - Of the three which were uncontrolled, two reported that quality of life declined in the first few months after treatment but then returned to baseline levels,[2][3] and one reported no overall changes[4].

  - The fourth study, by Katz et al, was a retrospective comparison of quality of life between surgery and SABR (Table 1).[5] The authors compared men who had undergone radical prostatectomy at ten Spanish hospitals with another group who had SABR at a hospital in New York. They reported that the men who had SABR had smaller and briefer declines in quality of life related to urinary symptoms, and avoided the loss of sexual quality of life that followed prostatectomy. There was a larger and more prolonged decline in bowel quality of life after SABR.

    Katz et al's study is unreliable. The two groups were too dissimilar for a comparison between them to be valid. The men who received SABR were older, had lower prostate-specific antigen levels, lower Gleason scores (a measure of tumour grade), earlier stage, lower risk tumours and smaller prostates. The quality of life of the two groups differed significantly at baseline, and the men who received SABR were also more likely to use sildenafil for erectile dysfunction. These important differences, rather than the effects of the treatments, may well explain the reported results.

    There may also be cultural or linguistic factors confounding this research. The use of a questionnaire in a different language and continent may give rise to spurious differences in response that would not appear in a single homogenous group of respondents.

We found one controlled study reporting oncological outcomes published since Tan et al's search date of January 2012 (Table 1).[6] Katz and Kang compared SABR with or without external beam radiotherapy in men with high-risk non-metastatic prostate carcinoma, and reported that five-year biochemical disease-free survival was 68% overall, and dd not differ significantly between the two groups.

This study may suggest that SABR alone is as effective SABR plus external beam radiotherapy, but needs to be interpreted with caution. It is of limited relevance and validity:

- The results of using SABR plus external beam radiotherapy lie outside the scope of this review. The first question to address is whether SABR should be used at all.
- The study was not randomised, and may be biased. Katz and Kang do not report how men were allocated to treatment. The two groups differed in potentially important ways. Most significantly, men who received only SABR had lower baseline prostate-specific antigen levels, suggesting their disease was less advanced. The authors attempted to adjust for this in their multivariate analysis, but treated the variable as dichotomous not continuous, a potentially less effective approach.
- The authors do not report a power calculation. Their analysis may have lacked statistical power and produced a false negative result.

We found one controlled study of treatment toxicity published since January 2012.[7] It is summarised in section 4.4 below.

We found no other controlled studies.

We found thirteen uncontrolled studies not included in Tan et al's systematic review. We excluded studies with fewer than a hundred participants; including these small uncontrolled studies would have not provided any further information on the effectiveness of SABR relative to other treatments. This left three studies for inclusion, one of treatment efficacy (Table 1) [8] and two toxicity studies summarised below in section 4.4 [9][10].

- Katz and Kang reported results from 477 men treated at a hospital in New York.[8] Earlier results from this cohort were included in Tan et al's review. Katz and Kang reported seven-year actuarial biochemical disease-free survival of 93.7% and overall survival of 85%.

4.2 Trials in progress

We searched clinicaltrials.gov and found five studies randomising men between SABR and other treatments:

- The Prostate Advances in Comparative Evidence (PACE) trial is based in the UK. Men for whom surgery is feasible are randomised to either prostatectomy or prostate SABR; other men are randomised to either conventionally fractionated radiation therapy or prostate SABR (NCT01584258). This trial is recruiting now.
- A comparison of conventional radiotherapy with stereotactic irradiation plus hyaluronic acid injection in the space between the prostate and the rectum to preserve the rectal wall from high doses of irradiation (NCT02361515). This trial is not yet open for recruitment.
- A comparison of SABR and IMRT in Hong Kong, now recruiting (NCT02339701)
- The Miami BLaStM Trial, which compares a form of stereotactic radiotherapy with more conventional radiotherapy (NCT02307058). This trial is now recruiting.
- A trial of conventional IMRT versus SABR (NCT01794403), now recruiting in the United States.

Table 1: Studies of SABR for prostate cancer

Study	Patients	Intervention	Comparator	Outcomes	Comments
Katz et al [5] 10 Spanish hospitals and one in Mineola, United States	Men receiving SABR had T1c or T2b prostate cancer and were treated at Mineola. Men receiving surgery had T1 or T2* prostate cancer, no previous transurethral resection and no hormonal therapy, and were treated at one of 10 hospitals in Spain.	SABR 35 or 36.25 Gy in 5 daily fractions, n = 216. Median age 69 years	Radical retropubic prostatectomy, with nerve-sparing** at the surgeon's discretion, n = 123. Median age 65 years	*At baseline* Urinary quality of life (QoL***): SABR 89.3, surgery 95.3, P < 0.0001. Sexual QoL: SABR 57.8, surgery 52.6, P < 0.004. Bowel QoL: SABR 95.5, surgery 96.4, P < 0.14. *After treatment, measured at 3 weeks, 5, 11, 24 and 36 months (SABR) and 1, 3, 6, 12, 24 and 36 months (surgery) (exact data not reported):* Urinary QOL: SABR: declined significantly at 3 weeks but at 5 months and thereafter was similar to baseline; surgery: declined significantly at 1 month, with only partial recovery thereafter. Sexual QoL: SABR: stable throughout; surgery: significant decline at 1 month with partial recovery thereafter, but significantly below baseline throughout.	Severe confounding: men receiving SABR were older (P < 0.0001), had lower prostate-specific antigen levels† (P < 0.0001), lower Gleason scores†† (P = 0.005), earlier stage (P < 0.0001), lower risk (P < 0.0001) and had smaller prostates (P = 0.005). They were also more likely to use sildenafil to for erectile dysfunction.

Study	Patients	Intervention	Comparator	Outcomes	Comments
				Bowel QoL: SABR: declined significantly until 12 months, after that recovering to baseline; surgery: significant decline at 1 month with recovery thereafter.	
Katz and Kang [6] Mineola, United States	97 men with organ-confined prostate cancer Mean age 70 years	External beam radiotherapy (EBRT) 45 Gy in 25 daily fractions followed at 2 weeks by 18, 19.5 or 21 Gy of SABR in 3 fractions (n=45)	SABR 35 or 36.25 Gy in 5 fractions, frequency not reported (n=52)	Median follow-up 60 months. 5-year biochemical disease-free survival: 68% overall, arm-specific results not reported (P = 0.86). Prostate-specific antigen†: no significant difference except at 3 months (lower with EBRT, P = 0.041). EBRT was not predictive of biochemical disease-free survival on multivariate analysis (P = 0.76). Quality of life: no significant differences.	Men receiving SABR were older (P < 0.039) and had lower prostate-specific antigen levels† (P = 0.0056).
Katz and Kang [8] Mineola, United States	477 men with low- and intermediate risk non-metastatic prostate cancer Median age 69 years	SABR 35 or 36.25 Gy in 5 daily fractions 51 men also had androgen deprivation therapy	Uncontrolled	Median follow-up 72 months 7-year actuarial biochemical disease-free survival 93.7%. Overall survival 85%. Local failure 0.9% of low-risk men and 2.6% of intermediate-	This cohort overlaps with Katz et al above [6]

Study	Patients	Intervention	Comparator	Outcomes	Comments
				risk men	
Yu et al [7] United States	55,176 men with early prostate cancer receiving treatment funded by Medicare	SABR, dose not specified (n = 1335)	IMRT, at least 4 fractions (n = 53,841)	Genito-urinary toxicity: 6 months odds ratio (OR†††) 1.29, 95% confidence interval (CI) 1.05 to 1.53, P = 0.009; 12 months OR 1.23, 95% CI 1.03 to 1.43, P = 0.01; 24 months OR 1.38, 95% CI 1.12 to 1.63, P = 0.001. Gastro-intestinal toxicity: 6 months OR 1.42, 95% confidence interval (CI) 1.00 to 1.85, P = 0.02; 12 months OR 1.06, 95% CI 0.82 to 1.29, P = 0.62; 24 months OR 0.92, 95% CI 0.71 to 1.12, P = 0.49. All other toxicities: no significant differences.	The study is subject to potential confounding. However, this would most likely have biased it in favour of IMRT, as IMRT patients were more likely to have androgen-deprivation therapy and therefore probably had higher risk disease. Some lower 95% confidence intervals are close to 1 with significant P-values, because of the large size of this study.

* T1 tumours are too small to be seen on scans or felt during examination of the prostate. They are diagnosed by needle biopsy, after finding a raised prostate-specific antigen level. T2 tumours are palpable but completely inside the prostate gland.

** Urologists can attempt to avoid or minimise nerve damage during prostatectomy, in an effort to preserve continence and potency.

*** Measured with the Expanded Prostate Cancer Index Composite (EPIC) score, which ranges from 0 to 100, higher scores indicating better QoL.

† A measure of disease extent

†† A measure of tumour grade (how aggressively malignant a tumour appears on microscopic examination)

††† Odds ratio > 1 indicates higher risk with SABR.

4.3 Evidence of cost-effectiveness

We found three studies of the cost effectiveness of SABR for prostate cancer:

- Hodges et al used Markov modelling to estimate the cost effectiveness of SABR and IMRT for organ-confined prostate cancer in a man of 70 years.[11] The authors assumed the two treatments were equally efficacious in terms of progression-free survival, and produced equal quality of life; the latter assumption is not compatible with the subsequent findings of Yu et al (see section 4,4 below).[7]. Costs were based on the US health care system in 2010. IMRT cost $29,530 (£19.400) and SABR $14,315 (£9400).

  It followed from these assumptions that the lower cost of IMRT yielded a lower cost per quality-adjusted life-year (QALY) (IMRT $35,431 (£23,300) versus $22,152 (£14,600) for SABR). Hodges et al varied their assumptions using sensitivity analysis, but SABR had an incremental cost effectiveness ratio of less than $50,000 in 66% of iterations.

  The senior author of this paper had received research funding from Accuray Incorporated, a manufacturer of stereotactic radiotherapy equipment.

- Sher et al's approach was similar to that of Hodges et al.[12] They derived their estimates of treatment efficacy and toxicity from published sources; it is not clear how they reconciled disparate results. Costs were from the 2012 Medicare tariff. The base case analysis indicated that IMRT yielded slightly more QALYs than SABR, but was also more expensive, with costs per QALY of $3,400 (£2200), compared with $2600 (£1700) for robotic SABR and $1700 (£1100) for non-robotic SABR. Sensitivity analysis indicated that SABR was cost-effective under most sets of parameter assumptions.

- Parthan et al also published a similar analysis, which also included proton beam therapy.[13] They based their assumptions about treatment efficacy on uncontrolled studies, which they meta-analysed without assessing heterogeneity. Costs were based on the US Medicare tariff.

  Like Hodges et al, Parthan et al concluded that SABR was the most cost effective treatment, with a cost per QALY of $3100 (£2000). IMRT and proton beam therapy had incremental costs per QALY versus SABR of $8195 (£5400) and $46,560 (£30,600). Sensitivity analysis made little difference, with SABR more cost-effective than IMRT and proton beam therapy in 75% and 94% of simulations respectively.

  Parthan et al is affected by a serious conflict of interest. The analysis was paid for by Accuray and one of the authors, responsible for part of the modelling, was an employee of the company.

These studies reach similar conclusions: that the lower costs of SABR (related to the lower number of fractions) lead to it to have better apparent cost effectiveness that IMRT. However, the analyses have a number of limitations:

- They are based on US healthcare costs, which differ significantly from those in the NHS.
- It is not clear how the extra capital costs of SABR equipment is modelled. All the studies assume that the payment under Medicare equals the true cost to the health care system of each treatment approach, rather than establishing the cost by bottom-up addition.
- The data on efficacy and toxicity come from uncontrolled studies. If men in the various studies differed in ways that influenced the probabilities of these events, then the studies' results cannot be validly compared, and the cost effectiveness analyses are unreliable.
- The analyses only compare SABR with other forms of radiotherapy. Early prostate cancer can also be treated with surgery, hormonal treatment and active monitoring, and these may be more cost effective than any form of radiotherapy.
- Not all baseline assumptions were compatible with, Yu et al's large and reliable analysis of the adverse effects of SABR and IMRT.[7]
- Some studies are affected by conflicts of interest.

4.4 Safety

Adverse urinary effects of SABR include urinary frequency and urgency, urinary retention, haematuria and urethral stricture. Rectal adverse effects include urgency and/or frequency of defecation and rectal bleeding.

- Tan et al's systematic review reported toxicity results from the 12 studies which included data on adverse effects of treatment, from a total of 921 participants.[1] The commonest form of acute toxicity was urinary, with grade 1 (least severe) adverse effects reported in 20% to 74% of participants. Grade 2 toxicity occurred in 5% to 42%; only three studies reported grade 3 toxicity, in a total of five (0.5%) of participants. There were no grade 4 or 5 events reported.

  Grade 1 acute rectal toxicity occurred in 3% to 75% of participants and grade 2 in 0% to 27%; there were no reports of more severe acute rectal toxicity.

  All 14 studies reported late toxicity, in 1100 participants. Grade 1 late urinary toxicity was reported in 0% to 44% of participants, and grade 2 in 0% to 29%. There were 14 participants with grade 3 toxicity (1.2%). Again, there were no grade 4 or 5 events reported.

  Late grade 1 rectal toxicity rates ranged from 0% to 35%, and grade 2 from 0% to 11%. Three participants suffered grade 3 late rectal toxicity and two grade 4 toxicity.

- Yu et al's study was published after Tan et al's search date (Table 1).[7] They used a comprehensive database of Medicare claims to compare adverse effects after SABR and intensity-modulated radiotherapy (IMRT). They identified men with early-stage prostate cancer aged 66 to 94 years who received one of these forms of radiotherapy as primary treatment.

  The study was large, including 53,841 men who had IMRT and 1335 who had SABR. The groups were dissimilar: SABR patients were younger, healthier, from higher income areas and less likely to have androgen-deprivation therapy, possibly indicating less aggressive disease. To reduce the consequent confounding effects, Yu et al matched each SABR patient with two IMRT patients for age, ethnicity, metropolitan residence, comorbidity, receipt of androgen-deprivation therapy, influenza vaccination (a marker of access to primary care), previous visit to a primary care provider and income. The analysis was confined to Medicare claims related to treatment toxicity.

  SABR was associated with more genito-urinary toxicity than IMRT at six, twelve and twenty-four months after treatment (Table 1). After two years, 44% of men who had had SABR had made a claim indicative of genito-urinary toxicity, compared with 36% of IMRT patients. Most of the extra toxicity from SABR was from the urethra and bladder, with a higher incidence of claims for diagnostic procedures for urinary incontinence and obstruction, and for the treatment of urethritis, urethral stricture and obstruction.

  Gastro-intestinal toxicity was also more common after SABR than after IMRT in the first six months, though no specific pattern of toxicity was evident.

- Arscott et al, also published since January 2014, reported an uncontrolled study of urinary obstruction after SABR for prostate cancer.[9] They found that obstructive voiding symptoms became more common at one month after treatment, but rates usually returned to pre-treatment levels within three months. Seven percent of the 269 men studied felt that weak urinary stream and/or incomplete emptying was still a problem two years after treatment.

- Bhattasali et al, also published since January 2014, reported that urinary and bowel symptoms became more common in the first month after SABR in the 228 men studied.[10] There was a further and more prolonged period of symptoms between nine and eighteen months, with a partial recovery by two years.

4.5 Summary of section 4

We found no randomised trials of SABR for prostate cancer, though several are in progress.

We found only one unrandomised controlled study of the efficacy of SABR.[6] Because of the use of SABR in both arms of the trial, a potentially ineffective

approach to adjustment for confounders and possible lack of power, this study is of limited value.

There are many uncontrolled studies which indicate the prognosis of men with prostate cancer treated with SABR, but shed no light on its performance relative to other treatments.

A large and well-controlled study reported that SABR was associated with more genito-urinary and gastro-intestinal adverse effects than IMRT.[7] Uncontrolled studies also indicate that SABR reduces quality of life with gradual, and in some cases only partial, recovery.

Health economic analyses from the United States indicate that SABR is less expensive than IMRT. If it is also equally effective and no more toxic, it is therefore more cost effective than IMRT. However, these analyses have a number of limitations that restrict their relevance and reliability.

5 Cost and activity

No cost or activity data were available.

6 Equity issues

We identified no specific equity issues.

7 Discussion and conclusions

We found little evidence specific to men unsuitable for surgery.

More generally, there is evidence from uncontrolled studies indicating that SABR is a feasible and acceptable treatment for prostate cancer. It can be delivered over fewer fractions than IMRT, which makes it more convenient for patients.

The absence of reliable, appropriately controlled studies makes it impossible to assess the effectiveness of SABR versus other treatments.

The adverse effects of SABR have an immediate and in some cases sustained effect on quality of life; these appear to be more common than after IMRT.

The cost of SABR depends on the price of equipment and rates of use and of depreciation. There are apparent savings from the reduced number of treatment sessions, but the studies from the United States which indicate that SABR is more cost effective than IMRT are of questionable reliability and relevance to the NHS.

Several randomised trials of SABR versus IMRT are in progress. This indicates the current clinical uncertainty about SABR's value and also suggests that policy-making will rest on more secure foundations once the results of these trials are available.

1. What is the clinical effectiveness of stereotactic ablative body radiotherapy for prostate cancer which is considered not suitable for surgery (because of medical co-morbidity or because lesion is inoperable), compared to best standard care?

   We found little evidence specific to men unsuitable for surgery.

   More generally, there is evidence from uncontrolled studies indicating that SABR is feasible and more convenient than IMRT. There is no reliable evidence that it is more effective, and reason to believe it produces more adverse effects.

   Randomised trials now recruiting are likely to reduce the uncertainty about SABR's performance relative to IMRT in treating prostate cancer.

2. What is the cost effectiveness of stereotactic ablative body radiotherapy for prostate cancer which is considered not suitable for surgery (because of medical co-morbidity or because lesion is inoperable), compared to best standard care?

   We found little evidence specific to men unsuitable for surgery.

   More generally, if one is willing to assume that SABR is less expensive than IMRT, equally effective and no more toxic, then it is more cost effective than IMRT. However, none of these assumptions can be accepted confidently on the basis of the evidence that we found.

8 Search Strategy (search date March 2015)

Population	Intervention	Comparator	Outcomes	Studies
1. Adults (18 years or over) with prostate cancer who are not suitable for surgery because of medical co-morbidity	Stereotactic Ablative Body Radiotherapy (SABR)	Best supportive care	Clinical effectiveness • Survival • Adverse events/complications • No of treatments • Quality of life (including patient self-reported outcome measures)	Meta-analyses Systematic reviews Randomised controlled trials Prospective non-randomised clinical study

or because lesion is technically inoperable.			Cost/cost-effectiveness Including resource utilisation, attendances Any other outcomes	Other clinical study* Conference abstracts* Health economics studies/models

1. Lung Neoplasms/

2. (sbrt or sabr).ti,ab.

3. Radiosurgery/

4. (stereotac* adj3 (radiother* or radiat* or irradiat* or radiosurg*)).ti,ab.

5. 2 or 3 or 4

6. Neoplasm Recurrence, Local/ and (Pelvic Neoplasms/ or exp nose neoplasms/ or exp pharyngeal neoplasms/ or exp Spinal Neoplasms/ or exp abdominal neoplasm/ or exp uterine neoplasms/)

7. Retreatment/ and (Pelvic Neoplasms/ or exp nose neoplasms/ or exp pharyngeal neoplasms/ or exp Spinal Neoplasms/ or exp abdominal neoplasm/ or exp uterine neoplasms/)

8. ((retreat* or re-irradiat* or reirradiat*) and ((pelvis or pelvic or nose or nasal or pharynx or pharyngeal or nasopharyn* or spine or spinal or abdomen or abdominal or gynaecolog* or gynecolog* or uter*) adj2 (cancer? or neoplasm? or carcinoma? or tumo?r?))).ti,ab.

9. ((residual or recur*) and ((pelvis or pelvic or nose or nasal or pharynx or pharyngeal or nasopharyn* or spine or spinal or abdomen or abdominal or gynaecolog* or gynecolog* or uter*) adj2 (cancer? or neoplasm? or carcinoma? or tumo?r?))).ti,ab.

10. exp Liver Neoplasms/

11. Cholangiocarcinoma/

12. ((liver or hepatic or hepatocell*) adj2 (cancer? or neoplasm? or carcinoma? or tumo?r?)).ti,ab.

13. cholangiocarcinoma?.ti,ab.

14. exp Prostatic Neoplasms/

15. ((prostate or prostatic) adj2 (cancer? or neoplasm? or carcinoma? or tumo?r?)).ti,ab.

16. Spinal Cord/ and Arteriovenous Malformations/

17. Spine/ and Arteriovenous Malformations/

18. Central Nervous System Vascular Malformations/

19. ((spine or spinal or central nervous system or cns) adj3 (arteriovenous malformation? or avm?)).ti,ab.

20. Meningioma/

21. ((spine or spinal or central nervous system or cns) adj3 meningioma?).ti,ab.

22. Neurilemmoma/

23. ((spine or spinal or central nervous system or cns) adj3 schwannoma?).ti,ab.

24. exp Kidney Neoplasms/

25. ((renal or kidney*) adj3 (cancer* or neoplas* or carcinoma* or malignan*)).ti,ab.

26. exp Lung Neoplasms/

27. ((lung or pulmonary) adj3 (cancer? or carcinoma? or neoplas* or tumo?r? or malignan*)).ti,ab.

28. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27

29. 5 and 28

30. limit 29 to (english language and yr="2014 -Current")

31. limit 30 to "reviews (maximizes specificity)"

32. limit 30 to ("economics (maximizes sensitivity)" or "costs (maximizes sensitivity)")

33. limit 30 to "therapy (maximizes sensitivity)"

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Competing Interest

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