Risk of subsequent primary cancers after carbon ion radiotherapy, photon radiotherapy, or surgery for localised prostate cancer: a propensity score-weighted, retrospective, cohort study

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Summary

Background The risk of subsequent primary cancers in patients with prostate cancer after treatment with photon radiotherapy is small in absolute numbers, but it is higher than that after surgical treatment. Carbon ion radiotherapy has a theoretically lower risk of inducing secondary malignancies than photon radiotherapy, but this risk has not been investigated in practice because of the low number of facilities offering such therapy worldwide and the limited data on long-term follow-up because the therapy has only been available since 1994. We aimed to analyse the risk of subsequent primary cancers after treatment with carbon ion radiotherapy in patients with localised prostate cancer and to compare it with that after photon radiotherapy or surgery in this setting.

Methods In this retrospective cohort study, we reviewed records of patients who received carbon ion radiotherapy for prostate cancer between June 27, 1995, and July 10, 2012, at the National Institute of Radiological Sciences (NIRS) in Japan. We also retrieved the records of patients diagnosed and treated for prostate cancer between Jan 1, 1994, and Dec 31, 2012, from the Osaka Cancer Registry. Eligible patients had histologically confirmed localised prostate cancer and a minimum follow-up of at least 3 months; no age restrictions were applied. We excluded patients with metastasis, node-positive disease, or locally invasive (T4 stage) prostate cancer, those with previous or synchronous malignancies, and those who received previous radiotherapy or chemotherapy. We did a multivariable analysis to estimate predictors of subsequent cancers after carbon ion radiotherapy treatment. We also used propensity score inverse probability weighting to retrospectively compare the incidence of subsequent cancers in patients with localised prostate cancer treated with carbon beams, photon radiotherapy, or surgery.

Findings Of 1580 patients who received carbon radiotherapy for prostate cancer at the NIRS, 1455 (92%) patients met the eligibility criteria. Of 38 594 patients with prostate cancer identified in the Osaka registry, 1983 (5%) patients treated with photon radiotherapy and 5948 (15%) treated with surgery were included. Median follow-up durations were 7·9 years (IQR 5·9–10·0) for patients who received carbon ion radiotherapy (after limiting the database to 10-year maximum follow-up), 5·7 years (4·5–6·4) for patients who received photon radiotherapy, and 6·0 years (5·0–8·6) for those who received surgery. 234 subsequent primary cancers were diagnosed in the carbon ion radiotherapy cohort; some patients developed several tumours. On multivariable analysis, age (p=0·0021 for 71–75 years *vs* ≤60 years; p=0·012 for >75 years *vs* ≤60 years) and smoking (p=0·0005) were associated with a higher risk of subsequent primary cancers in patients treated with carbon ion radiotherapy. In the propensity score-weighted analyses, carbon ion radiotherapy was associated with a lower risk of subsequent primary cancers than photon radiotherapy (hazard ratio [HR] 0·81 [95% CI 0·66–0·99]; p=0·038) or surgery (HR 0·80 [0·68–0·95]; p=0·0088), whereas photon radiotherapy was associated with a higher risk of subsequent primary cancers than surgery (HR 1·18 [1·02–1·36]; p=0·029).

Interpretation Our analysis suggests that patients with localised prostate cancer treated with carbon ion radiotherapy appear to have a lower risk of subsequent primary cancers than those treated with photon radiotherapy. Although prospective evaluation with longer follow-up is warranted to support these results, our data supports a wider adoption of carbon ion radiotherapy for patients with expected long-term overall survival or those with poor outcomes after receiving conventional treatments.

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Introduction

Awareness of the increased risk of subsequent primary cancers after antineoplastic therapy is crucial, especially for patients expected to be long-term survivors. Photon radiotherapy has been associated with an increased risk of subsequent primary cancers.[1] In patients with localised

Research in context

Evidence before this study

The risk of subsequent primary cancers after photon radiotherapy in patients with prostate cancer has been established. Carbon ion radiotherapy was first delivered in 1994 in Japan, but the long-term sequelae of this treatment have not been fully assessed yet, despite the expansion of carbon ion centres globally. We searched PubMed, until Nov 25, 2018, without date or language constraints using the terms "carbon ion radiotherapy (or radiation)", "subsequent primary cancer", "second primary cancer", "secondary malignant neoplasms", and "prostate cancer" to find relevant epidemiological studies on the incidence of subsequent primary cancers after carbon ion radiotherapy. No relevant studies on second cancer risk after carbon ion radiotherapy were retrieved.

Added value of this study

No studies with a large sample size or randomised data are available for carbon ion radiotherapy in any setting. However, in single-arm trials from single institutions and in retrospective studies, carbon ion radiotherapy has shown promising oncological outcomes with acceptable toxicities in selected patients with sarcoma, head and neck cancer, pancreatic cancer, and high risk prostate cancer, among others, who have poor outcomes with conventional treatments. Nevertheless, the risk of subsequent primary cancers after carbon ion radiotherapy is concerning, especially in patients with long life expectancy. In this Article, to our knowledge, we report for the first time the incidence of subsequent primary cancers after carbon ion radiotherapy in patients with localised prostate cancer.

Implications of all the available evidence

This study provides unique information about the risk of subsequent primary cancers after carbon ion radiotherapy in patients with localised prostate cancer that clinicians can discuss with their patients. Additionally, results from this hypothesis-generating study should encourage further research on subsequent malignancies and suggest that carbon ion radiotherapy might have an important role in treating patients with prolonged life expectancies.

prostate cancer, multiple studies have shown that photon radiotherapy carries a higher risk of subsequent primary cancers than surgery, although this increased risk is small in absolute numbers.[2,3] Although the risk of subsequent primary cancers after radiotherapy generally depends on sex, age at exposure, accumulated age after treatment, genetic predisposition, and lifestyle habits, it is also affected by radiation quality and dose-volume dosimetry.[4]

Carbon ion radiotherapy is a heavy ion radiation modality that has a stronger effect on tumour cells per physical dose (higher relative biological effect) and better dose distribution compared with photon-based therapies.[5] Carbon ion therapy was first delivered in Japan in 1994, and until 2002, the National Institute of Radiological Sciences (NIRS) was the only centre providing such treatments in Japan. For the treatment of prostate cancer, the 2006 clinical practice guidelines for prostate cancer in Japan[6] considered photon radiotherapy and surgery to be equivalent first-line treatments. Referral to carbon ion radiotherapy was mostly driven by patient request, whenever informed about that option by their physicians or media. Notably, neutrons produced during radiotherapy, either because of leaking from the treatment unit or nuclear fragmentation within the patient's body, are potent inducers of subsequent primary cancers.[7] However, comparative studies have shown that carbon ion radiotherapy produces fewer neutrons than protons or photons.[8,9] Although single-arm studies have suggested favourable oncological and toxicity outcomes with carbon ion radiotherapy,[10] concerns about long-term adverse events, especially subsequent primary cancers, have tempered enthusiasm for this promising therapy and have precluded its expansion.

According to the Particle Therapy Co-Operative Group (PTCOG), more than 20 000 patients have been treated globally using carbon ion radiotherapy up until 2016.[11] However, a detailed statistical analysis of the risk of subsequent primary cancers after carbon ion radiotherapy has not yet been done. We hypothesised that the risk of subsequent malignancies might be lower in patients receiving carbon ion radiotherapy than in those receiving photon radiotherapies. We had two goals for this study. The first was to describe the nature of subsequent primary cancers after carbon ion radiotherapy in patients with localised prostate cancer. The second was to compare the incidence of subsequent primary cancers in patients with localised disease treated with carbon ion radiotherapy, photon radiotherapy, or surgery as first-line treatment.

Methods

Study design and participants

In this retrospective cohort study, we used data from patients with localised prostate cancer treated at NIRS (based in Chiba, Japan) and from the Osaka Cancer Registry (covering the Osaka Prefecture, Japan) to investigate the risk of subsequent primary tumours after carbon ion radiotherapy, photon radiotherapy, and surgery.

We included patients with localised prostate cancer who had received passive-beam carbon ion radiotherapy at the NIRS between June 27, 1995, and July 10, 2012. Similarly, we identified patients diagnosed with prostate cancer between Jan 1, 1994, and Dec 31, 2012, from the Osaka Cancer Registry. For all patients, selection criteria were specified before analysis. Eligible patients had localised prostate cancer of any histological subtype and

	Carbon ion radiotherapy cohort (n=1455)
Age (years)	
Median (IQR)	68 (63–73)
Range	48–99
≤60	229 (16%)
61–65	336 (23%)
66–70	356 (24%)
71–75	344 (24%)
>75	190 (13%)
Smoking history	
Never	699 (48%)
Ever	741 (51%)
Unknown	15 (1%)
Smoking (pack-years)	
0	699 (48%)
1–30	272 (19%)
>30	330 (23%)
Unknown	154 (11%)
Alcohol use	
No	444 (31%)
Yes	996 (68%)
Unknown	15 (1%)
Charlson Comorbidity Index	
0	1184 (81%)
1	220 (15%)
2+	51 (4%)
Prostate cancer histology	
Adenocarcinoma	1454 (>99%)
Basal cell carcinoma	1 (<1%)
Cellular differentiation status	
Low grade	219 (15%)
Moderate	909 (62%)
High grade	313 (22%)
Unknown	14 (1%)
(Continued from previous column)	
Prostate cancer risk group (NCCN criteria)	
Low	184 (13%)
Intermediate	498 (34%)
High or very high	773 (53%)
Hormone therapy	
No	214 (15%)
Yes	1241 (85%)
Year of treatment	
1994–2000	115 (8%)
2001–05	329 (23%)
2006–10	731 (50%)
2011–12	280 (19%)
Total carbon ion radiotherapy dose (Gy relative biological effectiveness)	
51·6	46 (3%)
54	15 (1%)
57·6	878 (60%)
60	14 (1%)
63	205 (14%)
66	284 (20%)
72	13 (1%)
Number of carbon ion radiotherapy fractions	
12	46 (3%)
16	890 (61%)
20	519 (36%)
Follow-up (years)	
Median (IQR)	7·9 (5·9–10·3)

Data are n (%) unless otherwise specified.

Table 1: **Characteristics of patients in the carbon ion radiotherapy cohort**

at least 3 months of follow-up. No age restrictions were applied. Patients with previous or synchronous malignancies; those with metastatic, node-positive, or T4 stage disease or those who had received previous radiotherapy or chemotherapy; and those who had missing information on prostate cancer treatment history were excluded.

This retrospective study was approved by the institutional ethics review board in the Osaka International Cancer Institute (17–0006) and the NIRS in Japan (17–032). At the NIRS, all patients were asked to provide written, informed consent to permit the use of their data in clinical research and were given time to opt out from this study. Patient consent was not needed to use data from the Osaka Cancer Registry.

Procedures

For patients treated at NIRS, carbon ion radiotherapy was delivered as described elsewhere.[12] Briefly, the treatment field was limited to the prostate, with or without seminal vesicles, and without pelvic nodal irradiation. The median carbon ion radiotherapy dose was 57·6 Gy (relative biological effectiveness; range 51·6–72·0) delivered over a median of 16 fractions (range 12–20). For this cohort, we collected information from the NIRS database on patient demographics, smoking and alcohol habits, previous cancer diagnoses, and prostate cancer characteristics and treatments. Comorbidities at the time of initial visit were classified using the Charlson Comorbidity Index. Patients were followed up every 3–4 months for the first 2 years, and every 6 months for the subsequent 3 years. After 5 years, patients were followed up every 12 months, when possible. Data about subsequent primary cancers were gathered by reviewing clinical notes, pathology reports, radiology reports, and operative notes. Patients who were not followed up in person, either because they lived far away or because of other medical conditions, were contacted annually with specific questions about developing subsequent cancers, among other questions regarding prostate cancer recurrence, metastasis, and adverse events after treatment. Additional data on subsequent primary cancers were obtained by contacting other physicians, hospitals, or directly contacting patients or their families by telephone or mail, as needed. Missing data from patients were supplemented, with approval from the Ministry of Justice, from the Japanese family registry system, a nationwide registry that includes date and cause of death, and issuer of the death certificate.

For prostate cancer patients' records retrieved from the Osaka Cancer Registry, data included histological subtype, stage, method of detection, date of diagnosis, age at diagnosis, treatments (including previous surgery, endocrine therapy, chemotherapy, or radiotherapy), follow-up from time of diagnosis (duration and status at last follow-up [alive or dead]), and history of previous cancer diagnoses (classified as multiple primary cancers) and treatments. The registry strives to maintain a high follow-up (98–99%) by tracking each resident's vital status at 3 years, 5 years, and 10 years after initial cancer diagnosis, using death certificates and official resident registries. The registry does not collect information about smoking, alcohol use, family history of cancer, and other comorbidities. Regarding registry prostate cancer treatments, radiotherapy refers to external beam photon radiotherapy or brachytherapy, whereas surgery implies open or laparoscopic procedures for radical prostatectomy (no specific criteria are used or known for prostatectomy patients). No details about radiotherapy dose fractionation or field design are available. Registry patients who received both photon radiotherapy and radical prostatectomy were excluded because the timing and order of the treatments were not clearly defined. Registry data were last updated on Jan 19, 2018.

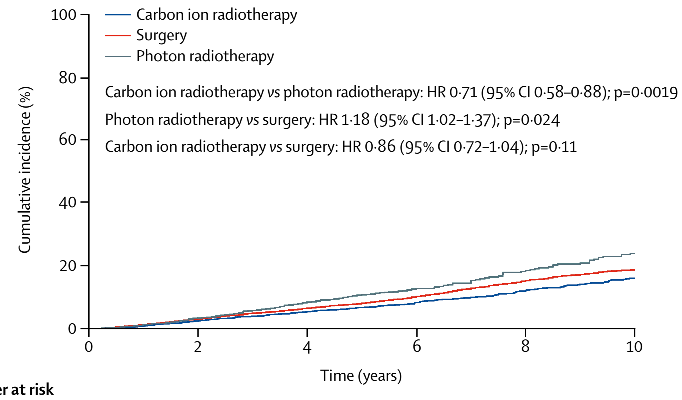
For patients who received carbon ion radiotherapy, follow-up started with radiotherapy initiation, whereas follow-up started after prostate cancer diagnosis for those patients whose treatment history was retrieved from the Osaka registry (because of the limitation on how data are collected in this registry), and continued until death, diagnosis of subsequent primary cancer, or the last day of follow-up (data cutoff Jan 31, 2018, for patients treated with carbon ion radiotherapy, or 10 years for those retrieved from the Osaka Cancer Registry), whichever occurred first. Because of the different follow-up criteria, to avoid overestimating subsequent primary cancers in the photon radiotherapy and surgery cohorts in the immediate period after prostate cancer diagnosis, malignancies identified within 90 days from follow-up initiation were not included.

Subsequent primary cancers were categorised (on the basis of anatomical location) as melanoma, head and neck (nasal cavity, buccal, lip, tongue, salivary, gum, oropharynx, nasopharynx, hypopharynx, larynx, and eye), thyroid, oesophagus, stomach, colon, rectum, liver, biliary (gall bladder or bile duct), pancreas, small bowel, lung, mesothelioma, breast, ureter, bladder, kidney, CNS, blood disorders (such as lymphoma, leukaemia, multiple myeloma, and other lymphoproliferative disorders),

	Patients with first subsequent primary cancer (%)	Univariate analysis*		Multivariable analysis†	
		HR (95% CI)	p value	HR (95% CI)	p value
Age (years)			0·0051		
≤60 (n=229)	19 (8%)	1 (ref)	··	1 (ref)	··
60–65 (n=336)	44 (13%)	1·52 (0·89–2·59)	··	1·46 (0·85–2·48)	0·17
66–70 (n=356)	49 (14%)	1·39 (0·82–2·36)	··	1·39 (0·82–2·36)	0·22
71–75 (n=344)	71 (21%)	2·23 (1·34–3·69)	··	2·22 (1·33–3·68)	0·0021
>75 (n=190)	35 (18%)	2·12 (1·21–3·71)	··	2·06 (1·18–3·62)	0·012
Smoking history			0·0021		
Never (n=699)	79 (11%)	1 (ref)	··	1 (ref)	··
Ever (n=741)	135 (18%)	1·64 (1·24–2·16)	··	1·64 (1·24–2·16)	0·0005
Unknown (n=15)	4 (27%)	1·77 (0·58–5·45)	··	1·69 (0·53–5·37)	0·37
Charlson Comorbidity Index			0·080		
0 (n=1184)	167 (14%)	1 (ref)	··	··	··
1+ (n=271)	51 (19%)	1·35 (0·98–1·85)	··	··	··
Alcohol use			0·76		
No (n=444)	63 (14%)	1 (ref)	··	··	··
Yes (n=996)	151 (15%)	0·99 (0·74–1·32)	··	··	··
Unknown (n=15)	4 (27%)	1·55 (0·51–4·74)	··	··	··
Prostate cancer risk group			0·90		
Low (n=184)	25 (14%)	1 (ref)	··	··	··
Intermediate (n=498)	73 (15%)	1·03 (0·77–1·38)	··	··	··
High (n=773)	120 (16%)	0·93 (0·60–1·43)	··	··	··
Prostate cancer differentiation			0·71		
Well (n=219)	31 (14%)	1 (ref)	··	··	··
Moderate (n=909)	137 (15%)	1·12 (0·77–1·65)	··	··	··
Poor (n=313)	49 (16%)	1·20 (0·77–1·88)	··	··	··
Unknown (n=14)	1 (7%)	0·52 (0·08–3·45)	··	··	··
Calendar year of treatment			0·11		
1994–2000 (n=115)	22 (19%)	1 (ref)	··	··	··
2001–05 (n=329)	81 (25%)	1·62 (1·02–2·56)	··	··	··
2006–10 (n=731)	94 (13%)	1·35 (0·84–2·16)	··	··	··
2011–12 (n=280)	21 (8%)	1·30 (0·70–2·42)	··	··	··
Hormone therapy			0·49		
No (n=214)	31 (14%)	1 (ref)	··	··	··
Yes (n=1241)	187 (15%)	1·14 (0·78–1·66)	··	··	··
Carbon radiation fraction number			0·60		
12 or 16 (n=936)	109 (12%)	1 (ref)	··	··	··
20 (n=519)	109 (21%)	0·96 (0·72–1·28)	··	··	··
Carbon radiation total dose (Gy relative biological effectiveness)			0·48		
<60 (n=939)	111 (12%)	1 (ref)	··	··	··
≥60 (n=516)	107 (21%)	0·93 (0·70–1·24)	··	··	··

HR=hazard ratio. *Using Gray's test. †Using cumulative incidence functions; includes only significant factors from the univariate analysis.

Table 2: **Risk factors for subsequent primary cancers after carbon ion radiotherapy**



Number at risk (number censored)						
Carbon ion radiotherapy	1455 (0)	1402 (7)	1317 (24)	1069 (216)	712 (512)	413 (764)
Surgery	5948 (0)	5702 (6)	5325 (82)	2978 (2147)	1541 (3393)	1389 (3404)
Photon radiotherapy	1983 (0)	1900 (0)	1727 (34)	782 (863)	241 (1357)	193 (1367)

Figure 1: **Cumulative incidence of subsequent primary cancers by treatment group**
Pairwise hazard ratios (HRs) were calculated from cumulative incidence function models before propensity score weighting, which also included age, calendar year, and hormone therapy as covariates.

testis, non-melanoma skin, and bone or soft tissue. Benign tumours and in-situ carcinomas were not included.

Statistical analysis

A formal power analysis was not done because of the retrospective nature of this study. We hypothesised that the risk of subsequent primary cancers is lower in patients with localised prostate cancer receiving carbon ion radiotherapy than those receiving photon radiotherapy. The entire follow-up period (until data cutoff on Jan 31, 2018) was included in the analysis of subsequent primary cancers for the carbon ion radiotherapy cohort. However, because follow-up in the Osaka Cancer Registry was limited to 10 years, when comparing carbon ion radiotherapy with photon radiotherapy or surgery, a subsequent primary cancer was defined as any invasive subsequent cancer diagnosed between 3 months and 10 years after prostate cancer treatment for carbon ion radiotherapy, and 3 months and 10 years after diagnosis for photon radiotherapy or surgery, unless it was considered recurrent or metastatic prostate cancer.

Since eligible treatments (carbon ion radiotherapy, photon radiotherapy, or surgery) were not assigned randomly, we did a propensity score inverse probability of treatment weighted analysis to balance baseline characteristics between treatment cohorts and evaluate the association between treatment type and the main outcome (subsequent primary cancer incidence). Propensity scores were estimated from available covariates (age, calendar year of treatment or diagnosis, and hormone therapy use) by use of multivariable logistic regression. The propensity-score-estimated densities for the test and reference cohorts were plotted for each pairwise comparison. The concordance statistic (c-statistic), a measure of goodness of fit in logistic regression, was used to test the appropriateness of the model. The inverse probability of treatment weights were defined as the inverse of the propensity score for patients in the test cohort and 1/(1–propensity score)—ie, the inverse of 1–propensity score—for patients in the reference cohort. Weight outliers of more than 20 or less than 0·05 were truncated to prevent sparse data. After calculating the weights, we used standardised differences of each covariate to evaluate the success of our model in creating balanced cohorts. Standardised differences of more than 0·1 were considered an indicator of imbalance for that particular covariate.

See Online for appendix

We did a competing risk analysis counting only first subsequent cancers as events and death as the competing risk to calculate the cumulative incidence of a subsequent primary cancer after treatment using the cumulative incidence function to model subdistribution hazards (Fine and Gray model).

We also did an analysis of cancer subsites, in which any site-specific cancer was included independently of whether it was the first, second, or third cancer. All cancers, excluding those diagnosed within 90 days of follow-up initiation, were included without assuming a latency period for subsequent primary cancer induction because the mechanisms of inducing malignancies after carbon ion radiotherapy are largely unknown.

Only pairwise comparisons (test *vs* reference group) were done: photon radiotherapy versus surgery (reference group), carbon ion radiotherapy versus photon radiotherapy (reference group), and carbon ion radiotherapy versus surgery (reference group). We used separate models for each pairwise comparison before propensity score weighting, or after weighting with or without additional covariates. We report hazard ratios (HRs) with 95% CIs from the competing risks analyses.

We did a sensitivity analysis to account for a 2-month hypothetical average delay in treatment for patients who underwent carbon ion radiotherapy by adding 2 months to their follow-up time, acknowledging the difference in follow-up start time between the carbon ion radiotherapy and control cohorts. The sensitivity analysis also accounted for patients who underwent carbon ion radiotherapy and had received neoadjuvant hormone therapy, by adding an additional delay of 3–6 months on average.

Standardised incidence ratios (SIRs) were calculated by dividing the observed number of cases of a subsequent primary cancer in each cancer site (limited to patients with more than ten observed cases) by the expected number of cases, using data published by the National Cancer Center (Tokyo, Japan), to compare the incidence of a particular subsequent primary cancer with that of the general population in Japan (appendix p 15).

All statistical tests were two-sided, and a p value of less than 0·05 was considered statistically significant for all comparisons. All analyses were done with SAS version 9.4. All references for statistical methods, including SAS codes, are included in the appendix (p 15).

	Photon radiotherapy *vs* surgery			Carbon ion *vs* photon radiotherapy			Carbon ion radiotherapy *vs* surgery		
	Photon radiotherapy (n=1628)	Surgery (n=6303)	Standardised difference	Carbon ion radiotherapy (n=974)	Photon radiotherapy (n=2464)	Standardised difference	Carbon ion radiotherapy (n=1439)	Surgery (n=5964)	Standardised difference
Median age (IQR), years	69 (64–73)	69 (64–72)	0·02	69 (64–74)	70 (64–74)	–0·06	69 (64–73)	68 (64–72)	0·06
Age (years)									
≤60	175 (11%)	710 (11%)	–0·02	120 (12%)	309 (13%)	–0·01	165 (12%)	763 (13%)	–0·04
61–65	332 (20%)	1243 (20%)	0·02	186 (19%)	449 (18%)	0·02	253 (18%)	1294 (22%)	–0·10
66–70	486 (30%)	1918 (30%)	–0·01	240 (25%)	596 (24%)	0·01	464 (32%)	1859 (31%)	0·02
71–75	459 (28%)	1730 (27%)	0·02	283 (29%)	691 (28%)	0·02	435 (30%)	1532 (26%)	0·10
>75	176 (11%)	702 (11%)	–0·01	145 (15%)	419 (17%)	–0·06	122 (8%)	516 (8%)	–0·01
Calendar year									
1994–2000	183 (11%)	560 (9%)	0·08	60 (6%)	171 (7%)	–0·03	450 (31%)	622 (10%)	0·53
2001–05	295 (18%)	1040 (16%)	0·04	157 (16%)	377 (15%)	0·02	310 (22%)	1171 (20%)	0·04
2006–10	696 (43%)	2834 (45%)	–0·04	484 (50%)	1190 (48%)	0·03	471 (33%)	2683 (45%)	–0·25
2011–12	454 (28%)	1869 (30%)	–0·04	273 (28%)	726 (30%)	–0·03	208 (14%)	1488 (25%)	–0·27
Hormone therapy									
Yes	432 (27%)	1755 (28%)	0·06	611 (63%)	1486 (60%)	–0·11	411 (29%)	2106 (35%)	0·31
No	1196 (73%)	4548 (72%)	–0·06	363 (37%)	978 (40%)	0·11	1028 (71%)	3858 (65%)	–0·31

Data are median (IQR) , n (%), or standardised difference.

Table 3: **Patients' characteristics according to treatment group after propensity score weighting with standardised differences**

Role of the funding source

The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. OM, TT, YN, AN, AS, HM, SY, TM, HT, IM, and TK had access to all the raw data. The corresponding author had full access to all the data and had the final responsibility for the decision to submit the manuscript for publication.

Results

The records of 1580 consecutive patients with localised prostate cancer who received carbon ion radiotherapy between June 27, 1995, and July 10, 2012 at the NIRS were retrieved; 1455 (92%) were eligible for analysis. Baseline characteristics of this cohort are shown in table 1. Of 38 594 patients with prostate cancer in the Osaka Cancer Registry diagnosed between Jan 1, 1994, and Dec 31, 2012, we identified 7931 (21%) eligible patients with localised disease treated with photon radiotherapy (n=1983) or surgery (n=5948). Median ages were 71 years (IQR 66–75) in the photon radiotherapy cohort and 68 years (64–72) in the surgery cohort (appendix p 2).

At a median follow-up of 7·9 years (IQR 5·9–10·3; absolute range 0·3–20·9), 234 second primary cancers were diagnosed in the carbon ion radiotherapy cohort (218 [15%] of 1455 patients developed at least one subsequent primary cancer), of which 217 (93%) were solid tumours and 17 (7%) were haematological malignancies (appendix p 1). The most common subsequent primary cancers for this cohort were stomach (44 [19%] of 234), lung (40 [17%]), colon (29 [12%]), and bladder (21 [9%]). The median time to first subsequent primary cancer for this cohort was 5·7 years (IQR 2·8–8·4; appendix p 2). In univariate analysis using death as a competing risk, increasing age (p=0·0051) and smoking (p=0·0021) were associated with a higher incidence of subsequent malignancy (table 2). However, Charlson Comorbidity Index, alcohol consumption, prostate cancer differentiation or risk category, year of treatment, use of hormone therapy, radiation dose, and number of radiotherapy fractions were not significant predictors of subsequent cancers (table 2). In multivariable analysis, both age and smoking remained significant (the remaining variables were not tested because they were not significant in the univariate models).

Next, we compared subsequent primary cancers between the carbon ion radiotherapy and the photon radiotherapy and surgery cohorts. We restricted the comparison to subsequent primary cancers occurring within 10 years of follow-up from the date of diagnosis or treatment of prostate cancer. Median follow-up was 7·9 years (IQR 5·9–10·0) for the carbon ion radiotherapy cohort, 5·7 years (4·5–6·4) for the photon radiotherapy cohort, and 6·0 years (5·0–8·6) for the surgery cohort. The numbers of subsequent primary cancers were 195 (184 [13%] of 1455 patients had at least one subsequent primary cancer within the 10 year follow-up limit) in the carbon ion radiotherapy cohort, 304 (273 [14%] of 1983 patients had at least one subsequent primary cancer) in the photon radiotherapy cohort, and 839 (747 [13%] of 5948 patients had at least one subsequent primary cancer) in the surgery cohort (appendix p 3–5). Similar to carbon ion radiotherapy, the most common subsequent primary

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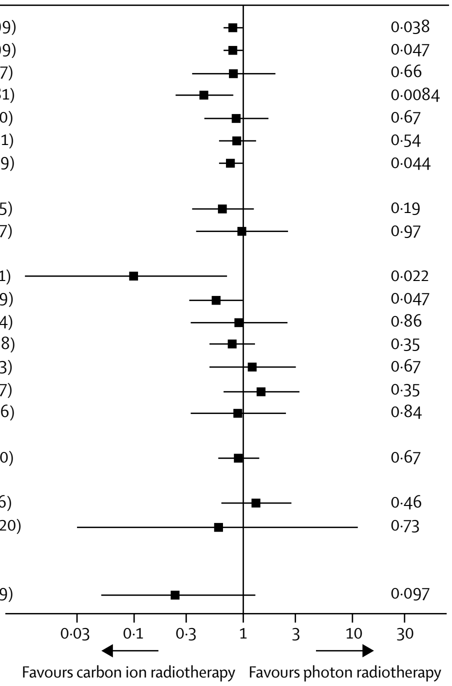
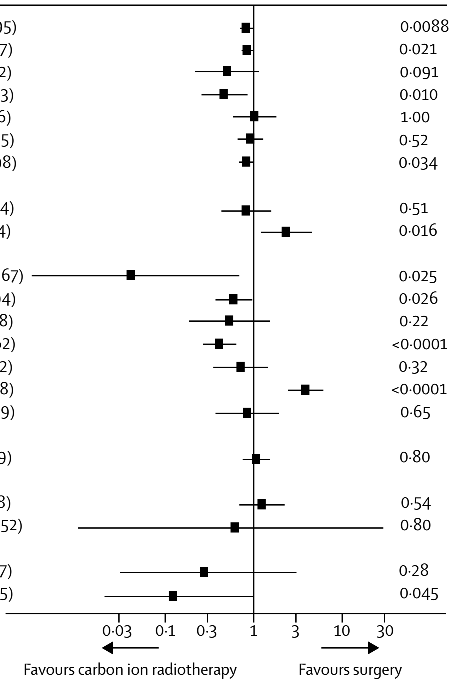
	Carbon ion radiotherapy (n=1455)	Photon radiotherapy (n=1983)	HR (95% CI)	p value
	Patients	Patients		
All subsequent cancers	184	273	0·81 (0·66–0·99)	0·038
Solid tumours	175	257	0·81 (0·66–0·99)	0·047
Haematological malignancies	11	17	0·82 (0·34–1·97)	0·66
Bladder or rectum cancers	19	51	0·44 (0·24–0·81)	0·0084
Above neck	11	19	0·87 (0·44–1·70)	0·67
Chest	38	63	0·88 (0·60–1·31)	0·54
Abdomen or pelvis	127	180	0·77 (0·60–0·99)	0·044
Genitourinary				
Bladder cancer	17	33	0·65 (0·34–1·25)	0·19
Kidney cancer	9	13	0·98 (0·37–2·57)	0·97
Gastrointestinal				
Rectal cancer	2	19	0·10 (0·01–0·71)	0·022
Colon cancer	27	47	0·57 (0·32–0·99)	0·047
Oesophageal cancer	11	9	0·92 (0·33–2·54)	0·86
Stomach cancer	38	53	0·80 (0·49–1·28)	0·35
Pancreatic cancer	11	10	1·22 (0·49–3·03)	0·67
Liver cancer	13	11	1·47 (0·66–3·27)	0·35
Biliary tract cancer	10	8	0·90 (0·33–2·46)	0·84
Chest				
Lung	27	52	0·91 (0·59–1·40)	0·67
Above neck				
Head and neck	9	10	1·32 (0·63–2·76)	0·46
CNS	1	2	0·60 (0·03–11·20)	0·73
Others				
Sarcoma	2	0	--	
Skin cancers	3	9	0·24 (0·05–1·29)	0·097



B

	Carbon ion radiotherapy (n=1455)	Surgery (n=5948)	HR (95% CI)	p value
	Patients	Patients		
All subsequent cancers	184	747	0·80 (0·68–0·95)	0·0088
Solid tumours	175	711	0·82 (0·71–0·97)	0·021
Haematological malignancies	11	43	0·49 (0·21–1·12)	0·091
Bladder or rectum cancers	19	87	0·45 (0·25–0·83)	0·010
Above neck	11	47	1·00 (0·57–1·76)	1·00
Chest	38	169	0·90 (0·64–1·25)	0·52
Abdomen or pelvis	127	514	0·81 (0·66–0·98)	0·034
Genitourinary				
Bladder cancer	17	43	0·80 (0·42–1·54)	0·51
Kidney cancer	9	24	2·27 (1·17–4·44)	0·016
Gastrointestinal				
Rectal cancer	2	44	0·04 (0·003–0·67)	0·025
Colon cancer	27	105	0·58 (0·36–0·94)	0·026
Oesophageal cancer	11	27	0·52 (0·18–1·48)	0·22
Stomach cancer	38	198	0·40 (0·26–0·62)	<0·0001
Pancreatic cancer	11	44	0·70 (0·34–1·42)	0·32
Liver cancer	13	37	3·78 (2·38–5·98)	<0·0001
Biliary tract cancer	10	24	0·83 (0·36–1·89)	0·65
Chest				
Lung	27	132	1·05 (0·73–1·49)	0·80
Above neck				
Head and neck	9	37	1·21 (0·67–2·18)	0·54
CNS	1	2	0·60 (0·01–28·52)	0·80
Others				
Sarcoma	2	7	0·27 (0·03–2·97)	0·28
Skin cancers	3	21	0·12 (0·02–0·95)	0·045



(Figure 2 continues on next page)

C

	Photon radiotherapy (n=1983) Patients	Surgery (n=5948) Patients	HR (95% CI)	p value
All subsequent cancers	273	747	1·18 (1·02–1·36)	0·029
Solid tumours	257	711	1·17 (1·01–1·36)	0·034
Haematological malignancies	17	43	1·05 (0·55–1·98)	0·89
Bladder or rectum cancers	51	87	2·28 (1·62–3·20)	<0·0001
Above neck	19	47	1·16 (0·66–2·05)	0·60
Chest	63	169	1·26 (0·94–1·69)	0·13
Abdomen or pelvis	180	514	1·15 (0·97–1·37)	0·12
Genitourinary				
Bladder cancer	33	43	3·08 (1·98–4·77)	<0·0001
Kidney cancer	13	24	1·38 (0·64–2·99)	0·41
Gastrointestinal				
Rectal cancer	19	44	1·49 (0·85–2·60)	0·16
Colon cancer	47	105	1·37 (0·95–1·95)	0·090
Oesophageal cancer	9	27	1·68 (0·86–3·28)	0·13
Stomach cancer	53	198	0·71 (0·50–1·01)	0·054
Pancreatic cancer	10	44	0·75 (0·36–1·58)	0·45
Liver cancer	11	37	1·18 (0·61–2·31)	0·62
Biliary tract cancer	8	24	1·02 (0·44–2·37)	0·97
Chest				
Lung	52	132	1·22 (0·87–1·71)	0·25
Above neck				
Head and neck	10	37	0·78 (0·37–1·65)	0·51
CNS	2	2	2·13 (0·24–18·8)	0·50
Others				
Sarcoma	0	7	..	..
Skin cancers	9	21	1·12 (0·48–2·63)	0·79

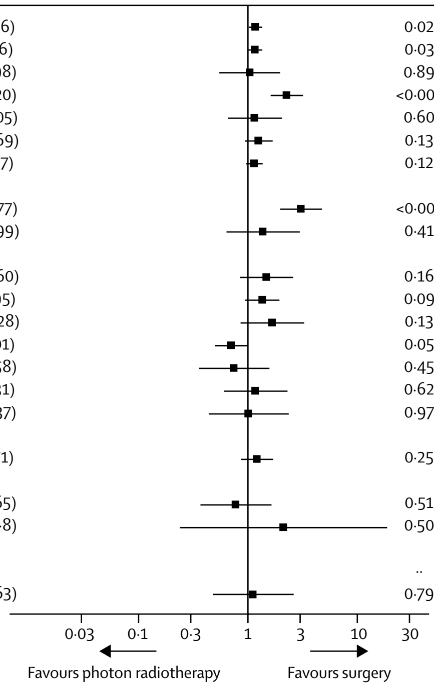


Figure 2: **Forest plots of the pairwise comparisons of subsequent primary cancers by treatment group after propensity score weighting**
(A) Carbon ion radiotherapy *vs* photon radiotherapy. (B) Carbon ion radiotherapy *vs* surgery. (C) Photon radiotherapy *vs* surgery. Hazard ratios (HRs) are from analysis of weighted treatment groups, whereas the shown number of patients who developed second cancers represents actual events from the original data before weighting.

cancers were in the stomach, lung, colon, and bladder in both control cohorts (appendix p 3–5).

We used different models to compare the risk of subsequent primary cancers in the three cohorts. Initially, we used a cumulative incidence function to model the subdistribution hazards for each pairwise comparison before propensity score weighting. The model included, in addition to paired treatments, age and calendar year (as continuous variables), and hormone therapy. The cumulative incidence of subsequent primary cancers at 9·9 years was 16·1% (95% CI 13·9–18·4) in the carbon ion radiotherapy group, 24·0% (20·5–27·6) in the photon radiotherapy group, and 18·7% (17·4–20·1) in the surgery group (figure 1). 94 (6%) of 1455 patients in the carbon ion radiotherapy cohort, 150 (8%) of 1983 patients in the photon radiotherapy cohort, and 408 (7%) of 5948 patients in the surgery cohort were dead at last follow-up without subsequent primary cancers. Pairwise comparisons showed a lower incidence of subsequent primary cancers in the carbon ion radiotherapy cohort than in the photon radiotherapy cohort, with no statistical difference between carbon ion radiotherapy and surgery. Photon radiotherapy, however, was associated with a higher risk of subsequent primary cancer than surgery (figure 1). Pairwise comparisons of all subsite specific subsequent primary cancers are shown in the appendix (p 6).

We built a propensity score logistic regression model using age, year of treatment initiation or of diagnosis, and use of hormone therapy as covariates to estimate standardised inverse probability treatment weights. The estimated probability density functions of the propensity score for the comparison groups and c-statistics values are shown in the appendix (p 7). The distribution of available covariates was adequately balanced in the three comparisons after propensity score weighting (table 3) compared with the unbalanced raw input (appendix p 8). We used the cumulative incidence function to account for deaths as a competing risk for each pairwise comparison after propensity score weighting (figure 2). Photon radiotherapy was associated with a higher risk of subsequent primary cancers than surgery, but the risk of subsequent primary cancers was lower after carbon ion radiotherapy than after photon radiotherapy and surgery (figure 2). The lower subsequent primary cancer risk in the carbon ion radiotherapy cohort compared with the photon radiotherapy group seems to be because of a

	Observed number of patients	Person-years of follow-up	Expected number of patients	SIR (95% CI)
Genitourinary				
Bladder				
Carbon ion radiotherapy	17	12 384·66	10·1	1·68 (0·93–2·56)
Photon radiotherapy	31	11 213·72	9·3	3·34 (2·16–4·51)
Surgery	41	39 478·07	28·2	1·45 (0·99–1·87)
Kidney or urinary tract				
Carbon ion radiotherapy	10	12 386·28	8·2	1·22 (0·55–2·12)
Photon radiotherapy	14	11 279·72	7·9	1·78 (0·92–2·83)
Surgery	37	39 467·50	23·9	1·55 (1·04–2·03)
Gastrointestinal				
Oesophagus				
Carbon ion radiotherapy	12	12 398·58	11·3	1·07 (0·52–1·77)
Photon radiotherapy	10	11 296·12	10·7	0·94 (0·43–1·63)
Surgery	23	39 548·59	35·4	0·65 (0·39–0·93)
Stomach				
Carbon ion radiotherapy	43	12 307·32	58·3	0·74 (0·49–0·93)
Photon radiotherapy	50	11 182·45	54·6	0·92 (0·65–1·15)
Surgery	197	38 943·70	174·3	1·13 (0·93–1·23)
Colon				
Carbon ion radiotherapy	29	12 324·65	28·2	1·03 (0·65–1·40)
Photon radiotherapy	47	11 199·67	26·3	1·79 (1·25–2·26)
Surgery	109	39 183·73	83·6	1·30 (1·02–1·49)
Liver				
Carbon ion radiotherapy	15	12 422·02	20·8	0·72 (0·38–1·13)
Photon radiotherapy	11	11 293·62	19·8	0·56 (0·26–0·95)
Surgery	39	39 489·89	64·6	0·60 (0·41–0·78)
Chest				
Lung				
Carbon ion radiotherapy	36	12 328·82	51·0	0·71 (0·47–0·93)
Photon radiotherapy	50	11 209·79	47·9	1·04 (0·74–1·31)
Surgery	146	39 286·76	145·4	1·00 (0·81–1·12)

SIR=standardised incidence ratio.

***Table 4:* Standardised incidence ratios for subsequent primary cancers after carbon ion radiotherapy, photon radiotherapy, or surgery for prostate cancer**

lower risk of abdominopelvic cancers, specifically those in the colon and rectum. These results were consistent in models after propensity score weighting using standardised weights, age, calendar year, and hormone therapy as covariates (appendix p 9). Results were also consistent in a sensitivity analysis accounting for the difference in follow-up time between carbon ion radiotherapy and control cohorts (appendix pp 10–11). To account for a potential latency period for subsequent primary cancer induction after radiotherapy, we repeated the analysis (with and without propensity score weighting) after excluding subsequent primary cancers that occurred before 2 years of follow-up (appendix p 12). Subsequent primary cancers of the bladder and rectum (analysed together) continued to be lower in the carbon ion radiotherapy cohort than in the photon radiotherapy cohort.

Finally, we used SIRs to compare the risk of specific subsequent cancers by site in any of the three cohorts compared with the risk of developing the same cancer in the Japanese population. The SIRs for specific subsequent primary cancers in the carbon ion radiotherapy, photon radiotherapy, and surgery cohorts are listed in table 4. We did not observe a higher subsequent primary cancer risk in the carbon ion radiotherapy cohort compared with that of the general population in any of the cancer sites, including bladder cancer (SIR 1·68 [95% CI 0·93–2·56]). However, bladder cancer risk was increased in patients who received photon radiotherapy compared to the general population (SIR 3·34 [95% CI 2·16–4·51]); patients who had surgery did not have an increased risk of subsequent primary bladder cancer compared with the general population (1·45 [0·99–1·87]).

Discussion

To our knowledge, this Article is the first report describing risk factors for developing subsequent primary cancers after carbon ion radiotherapy, and comparing the risk of subsequent primary cancers in these patients compared with those treated with photon radiotherapy or surgery. Our results suggest a potentially lower subsequent primary cancer risk after carbon ion radiotherapy than after photon radiotherapy, mostly driven by a reduced risk of solid tumours in the abdominopelvic region. These subsequent primary cancers could be either spontaneous or radiation-induced cancers because the cause of these malignancies was impossible to ascertain from the epidemiological data available.

The risk of subsequent primary cancers after photon radiotherapy has been described before.[1,4] However, photons have lower linear energy transfer than heavier particles such as carbon ions, which might impart a different subsequent primary cancer risk.[5] Preclinical studies that explored the link between heavy ion irradiation and subsequent primary cancers showed a high risk of solid tumour induction. However, these animal studies used ions and energies not typically used in clinical radiotherapy.[13–15] Preclinical or modelling studies using heavy particle qualities relevant to irradiation in humans are scarce, but available evidence indicates that risk is either lower than or similar to other radiotherapy modalities.[16–18] Admittedly, these studies are inconclusive, especially because carbon beams impart less neutron exposure than protons or photons.[9] A study by Yonai and colleagues[19] showed that, in patients with prostate cancer, the out-of-field dose equivalent was lower after passive beam carbon ion radiotherapy than after both 6-MV intensity-modulated radiotherapy or brachytherapy for organs within 40 cm of the target. A few retrospective epidemiological studies have investigated the risk of subsequent primary cancers after proton therapy, a low-linear energy transfer radiation modality compared with photon radiotherapy.[20] In particular, Chung and colleagues[21] compared a cohort of 558 patients who had received proton therapy with a matched patient cohort from the Surveillance, Epidemiology, and End Results (SEER) database treated with photons. Results suggested a lower risk of subsequent primary cancers in the proton therapy group than in those treated with photons. Although preliminary, these results combined with those from our study suggest a potentially lower incidence of subsequent primary cancers after particle therapy than photon radiotherapy. In addition to radiation modality and dosimetric considerations,[22] other patient-related factors, such as age and smoking, might affect the risk of subsequent primary cancers.[23] In agreement with this concept, we have shown that age and smoking were significant predictors of subsequent primary cancers after carbon ion radiotherapy.

Studying subsequent malignancies in patients with prostate cancer after carbon ion radiotherapy allowed us to select a large cohort of patients with expected long-term overall survival and follow-up, and use control groups of patients from the Osaka registry[24] who received a different treatment (at the NIRS patients with prostate cancer are only offered carbon ion radiotherapy). Unfortunately, a nationwide registry with long-term follow-up and data on second malignancies after radiotherapy is not currently available in Japan. A nationwide registry was started in 2016 but will need several years before its data are mature enough to allow the investigation of subsequent primary cancers.

Our study has several limitations. First, the photon radiotherapy cohort included a heterogeneous group of external beam and brachytherapy radiation treatments, and details about radiation dose fractionation or field design are not available. However, according to the 2004 radiotherapy treatment planning guidelines in Japan, pelvic irradiation is debatable even for high-risk patients, which is in accordance with the volumes used with carbon ion radiotherapy (prostate with or without seminal vesicles only).[25] Data on subsequent primary cancers after prostate only versus pelvic photon irradiation are scarce, but preliminary data from post-hoc exploratory analysis from the updated results of RTOG 9413, a large randomised study investigating the role of pelvic versus prostate only radiation, and neoadjuvant versus adjuvant hormonal therapy, suggest the incidence of subsequent cancers did not seem to differ between the groups.[26] Similarly, the exact external beam photon radiotherapy technique is unclear (two-dimensional *vs* three-dimensional conformal *vs* intensity-modulated radiotherapy), which has substantial implications for rectal or bladder doses and whole body exposure and, therefore, a different subsequent primary cancer induction risk.[27] Second, the induction of subsequent primary cancers depends, in addition to radiation characteristics, on other factors such as family history of cancer, environmental factors (sun and radiation exposure, human papillomavirus infection), habits (smoking, alcohol, exercise, diet), comorbidities (obesity, diabetes, immunosuppressive disorders), socio-economic status, and age. Unfortunately, the Osaka registry does not collect data about smoking, alcohol use, family history of cancer, or other comorbidities, which could have enriched our propensity score model. Given the restricted extent of the data available in the Osaka registry, our propensity score model covariates were limited to age, calendar year of treatment or diagnosis, and use of hormonal therapy. Although smoking data are unavailable in the control cohorts, more than half of the patients in the carbon ion radiotherapy cohort were either current or previous smokers. Shiota and colleagues[28] studied the effects of smoking on bladder cancer development in 754 patients undergoing photon radiotherapy versus surgery for prostate cancer from 2000 to 2013. They reported that 46% of all patients were either current or previous smokers. This percentage suggests that our carbon ion radiotherapy cohort had an adequate representation of smokers (51% *vs* 46%). Moreover, similar lung and head and neck cancer numbers among the three cohorts in this study suggest that baseline smoking characteristics were likely to be balanced.

Third, although data on socioeconomic factors are unavailable, patients receiving carbon ion radiotherapy should have the financial means (or private insurance) to cover treatment costs from 2003 onwards (before 2003 the cost was fully paid by the NIRS because all patients were treated within cost-free clinical trials). Hence, some might assume that those who receive carbon ion radiotherapy have higher socioeconomic status and are possibly healthier than patients in the control cohorts. However, Japan has a universal health-care coverage system providing citizens, including people with low income, access to health-care resources, thus reducing the effect of socioeconomic status on health outcomes. In addition, Guzzo and colleagues[29] have shown, in a study with more than 14 000 patients with prostate cancer undergoing prostatectomy, that the Charlson Comorbidity Index score was 0 or 1 in 98% of patients (similar to the 96% in our study). These numbers might indicate a similar comorbidity burden in our carbon ion radiation cohort as in surgical patients.[29]

Fourth, although the risk of developing subsequent primary cancers was similar between carbon ion radiotherapy and surgery before propensity score weighting, we observed lower subsequent primary cancer incidence with carbon ion radiotherapy than with surgery after weighting. A standardised difference of less than 0·1 in the carbon ion radiotherapy versus surgery comparison was more difficult to achieve, presumably because of inherent baseline differences in unmeasured covariates (eg, patients undergoing surgery do not typically receive hormone therapy). In addition, more urologist surveillance with cystoscopies, colonoscopies, or both might explain the higher risk of abdominopelvic subsequent primary cancers in the surgery cohort than in the carbon ion radiotherapy cohort.[30] Routine surveillance cystoscopies or colonoscopies are uncommon in patients treated by radiation oncologists. Eifler and colleagues[31] reported the causes of death in a large cohort of patients after radical prostatectomy and found lower mortality due to second malignancy than in the general population. Hence, some might even argue that a surgery control cohort might not be appropriate in these comparisons. Nevertheless, we decided to include it to show the internal validity of the Osaka Registry data by reproducing the higher risk of subsequent primary cancer after photon radiotherapy than after surgery.

Fifth, although we acknowledge that photon radiation-induced cancers usually require a latency period (2 years for haematological malignancies and 5 years for solid malignancies), we intentionally elected to report our results without allowing for a latency period because the mechanisms of subsequent primary cancer induction after carbon ion radiotherapy are unknown, and did a sensitivity analysis accounting for a 2-year latency, the results of which were not substantially different to our main results. Sixth, this study is also limited by its follow-up period of only 10 years, a limitation of the Osaka Registry database. With longer follow-up, the subsequent primary cancer incidence will increase in all three cohorts, potentially changing the results. Seventh, this study has some selection bias, because the patients who underwent carbon ion radiotherapy were from all over Japan, whereas controls were from a single prefecture (Osaka). Bias caused by differences in follow-up methods, including differences in follow-up start times across the three cohorts, might have also confounded our results. For the patients treated with carbon ion radiotherapy, we relied on an independent in-depth review of medical records and cause of death based on death certificates, whereas the Osaka Registry patients were tracked by the registry staff after 3 years, 5 years, and 10 years from diagnosis. Despite these limitations, SIRs, which compared subsequent primary cancer risk to cancer incidence in the overall Japanese population, did not show a higher risk of subsequent primary cancers in the carbon ion radiotherapy cohort. A detailed analysis of previous studies that investigated the risk of subsequent primary cancers after photon radiotherapy for prostate cancer (appendix p 13) show that these studies are commonly limited by short follow-up, inhomogeneous comparison cohorts and follow-up methods, and lack of adjustment for critical risk factors for subsequent primary cancer induction, similar to the limitations in our study. Finally, although the presented data are an important contribution to a growing body of knowledge in heavy ion therapy, their global practical value is limited because most clinicians do not have access to carbon ion radiotherapy. Clinicians rarely incorporate subsequent primary cancer risk when making decisions about prostate cancer treatment; however, life expectancies in this setting are expected to increase with men getting diagnosed at a younger age, new imaging modalities detecting early metastatic lesions, the new potential role of localised prostate radiotherapy in patients with metastatic disease, and also the substantial improvements in systemic therapies. All these factors will make the risk of subsequent primary cancers a real issue to long-term survivors.

In summary, despite the limitations of our study, our data suggest that the risk of subsequent primary cancer seems to be lower after carbon ion radiotherapy than after photon radiotherapy for patients with localised prostate cancer. This hypothesis-generating study requires further validation in prospective studies or from additional multinational datasets, in disease sites other than prostate cancer, especially in the setting of similar proton data.[21] If validated, these results should encourage a wider adoption of ion radiotherapy in the context of appropriate and cost-conscious patient selection.

Contributors

OM, YN, AN, AS, and HM did the literature search. OM and HM contributed to the study design. OM, YN, AN, AS, GK, and HM contributed to data collection and analysis. TT also contributed to data analysis. OM, TT, AS, GK, and HM participated in data interpretation. OM, TT, AS, GK, and HM contributed to writing the manuscript. GK and TM contributed to data collection, analysis, and interpretation, and writing the manuscript. HC, SY, HT, IM, and TK contributed to the study conceptualisation and design, data analysis and interpretation, writing of the manuscript, and overall supervision. All authors read and approved the final version.

Declaration of interests

We declare no competing interests.

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