Use of radiotherapy in patients with oesophageal, stomach, colon, rectal, liver, pancreatic, lung, and ovarian cancer: an International Cancer Benchmarking Partnership (ICBP) population-based study

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Summary

Background There is little evidence on variation in radiotherapy use in different countries, although it is a key treatment modality for some patients with cancer. Here we aimed to examine such variation.

Methods This population-based study used data from Norway, the four UK nations (England, Northern Ireland, Scotland, and Wales), nine Canadian provinces (Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario, Prince Edward Island, and Saskatchewan), and two Australian states (New South Wales and Victoria). Patients aged 15–99 years diagnosed with cancer in eight different sites (oesophageal, stomach, colon, rectal, liver, pancreatic, lung, or ovarian cancer), with no other primary cancer diagnosis occurring within the 5 years before to 1 year after the index cancer diagnosis or during the study period were included in the study. We examined variation in radiotherapy use from 31 days before to 365 days after diagnosis and time to its initiation, alongside related variation in patient group differences. Information was obtained from cancer registry records linked to clinical or patient management system data, or hospital administration data. Random-effects meta-analyses quantified interjurisdictional variation using 95% prediction intervals (95% PIs).

Findings Between Jan 1, 2012, and Dec 31, 2017, of 902 312 patients with a new diagnosis of one of the studied cancers, 115 357 (12·8%) did not meet inclusion criteria, and 786,955 were included in the analysis. There was large interjurisdictional variation in radiotherapy use, with wide 95% PIs: 17·8 to 82·4 (pooled estimate 50·2%) for oesophageal cancer, 35·5 to 55·2 (45·2%) for rectal cancer, 28·6 to 54·0 (40·6%) for lung cancer, and 4·6 to 53·6 (19·0%) for stomach cancer. For patients with stage 2–3 rectal cancer, interjurisdictional variation was greater than that for all patients with rectal cancer (95% PI 37·0 to 84·6; pooled estimate 64·2%). Radiotherapy use was infrequent but variable in patients with pancreatic (95% PI 1·7 to 16·5%), liver (1·8 to 11·2%), colon (1·6 to 5·0%), and ovarian (0·8 to 7·6%) cancer. Patients aged 85–99 years had three-times lower odds of radiotherapy use than those aged 65–74 years, with substantial interjurisdictional variation in this age difference (odds ratio [OR] 0·38; 95% PI 0·20–0·73). Women had slightly lower odds of radiotherapy use than men (OR 0·88, 95% PI 0·77–1·01). There was large variation in median time to first radiotherapy (from diagnosis date) by cancer site, with substantial interjurisdictional variation (eg, oesophageal 95% PI 11·3 days to 112·8 days; pooled estimate 62·0 days; rectal 95% PI 34·7 days to 77·3 days; pooled estimate 56·0 days). Older patients had shorter median time to radiotherapy with appreciable interjurisdictional variation (–9·5 days in patients aged 85–99 years *vs* 65–74 years, 95% PI –26·4 to 7·4).

Interpretation Large interjurisdictional variation in both use and time to radiotherapy initiation were observed, alongside large and variable age differences. To guide efforts to improve patient outcomes, underlying reasons for these differences need to be established.

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Research in context

Evidence before this study

We searched PubMed on Jan 31, 2023, without language or year of publication restrictions for population-based studies examining the use of radiotherapy in patients with the eight studied cancers in jurisdictions of more than one country. We used the search terms "radiotherapy use", "population-based", and "international comparison" and previous searches to derive a core group of so-called seeded papers. These were used to propagate the enquiry through searches of lead authors or keywords included in already identified papers, articles appearing in similar and cited by PubMed lists, and inspection of the 30 most relevant papers by means of inciteful.xyz graphs. We identified nine primary studies examining use of radiotherapy in up to eight international jurisdictions, typically within a single continent (Europe), for patients with four of the studied cancer sites (oesophageal–stomach, rectal, and pancreatic). Relevant available evidence has not formally quantified the size of interjurisdictional variation in radiotherapy use, or of related age inequalities, and did not encompass time to radiotherapy initiation.

Added value of this study

To our knowledge, this is the first study that establishes the frequency of radiotherapy use, alongside time to radiotherapy initiation, in patients diagnosed in the last decade with eight common cancers (oesophageal, stomach, colon, rectal, liver, pancreatic, lung, and ovarian) across international jurisdictions in multiple continents. We identified wide variation in radiotherapy use, and in age-related disparities, following broad jurisdictional patterns. The findings highlight the value of incorporating measures of radiotherapy use in international studies comparing cancer treatment and outcomes, and of introducing population-based surveillance of treatment patterns and related disparities both within and between countries.

Implications of all the available evidence

The findings highlight the need to understand the causes of international variation in radiotherapy use, alongside the possible implications of such variation for patient outcomes and international differences in cancer survival. Future work should examine tumour, patient, and health-care factors underlying radiotherapy use in different countries and health systems. Health-care factors to be examined should encompass potential differences in clinical guidelines and their implementation, service organisation, system capacity, health-care professional cultures, patient treatment preferences, and access to trial protocols. Incorporating measures of radiotherapy use in both international comparative survival studies and in routine, within-country, cancer surveillance is warranted.

Introduction

Variation between countries and subnational jurisdictions in the use and timeliness of different cancer treatments possibly contributes to international differences in cancer survival.[1–2] For many patients radiotherapy is a key type of cancer treatment modality, with indications that vary by cancer site, disease stage, and performance status. Previous evidence has documented variation in radiotherapy use between different patient groups or geographical regions within countries.[3–5] Health needs for radiotherapy are often not met, and radiotherapy services and research are often under-resourced.[6–8] Multicountry comparisons of radiotherapy use are sparse.[9,10]

When radiotherapy is used in a neo-adjuvant or adjuvant fashion, shorter time to treatment initiation is important for patient experience and represents a marker of system capacity and efficiency. So-called waiting time statistics often form part of performance measures within individual countries; however, multicountry evidence about variation in time to radiotherapy initiation is scarce.[11–13]

We have examined international variation in overall use and time to first radiotherapy treatment, and related interjurisdictional variation by age group, sex, and cancer site, as a step towards a more detailed understanding of international variation in cancer treatment.

The study forms part of the International Cancer Benchmarking Partnership, a collaboration of clinicians, policymakers, researchers, and data experts in seven countries (Australia, Canada, Denmark, Ireland, New Zealand, Norway, and the UK), seeking to explain cancer survival differences between high-income countries with comprehensive cancer registries, similar health system expenditure, and universal health care to help improve cancer care and outcomes globally.[1,14,15]

Methods

Data

The data used in this population-based study relate to Norway, the four UK nations (England, Northern Ireland, Scotland, and Wales), nine Canadian provinces (Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario, Prince Edward Island, and Saskatchewan), and two Australian States (New South Wales and Victoria) covered by high-quality population-based cancer registries (appendix p 3).[1,2] Radiotherapy use was ascertained from cancer registry records, linked as applicable to data from clinical or patient management systems, or hospital administration data (appendix p 4).

Inclusion criteria were a new primary diagnosis of oesophageal, stomach, colon, rectal, liver, pancreatic, lung, or ovarian cancer (based on International Classification of Diseases 10th revision definitions; appendix p 5) during the study period within the populations served by the participating cancer registries,

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See **Online** for appendix

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in patients aged 15–99 years at diagnosis, without site-sex discordance (applicable to ovarian cancer only), not registered solely from a death certificate, and without other primary cancer diagnosis occurring within 5 years before to 1 year after the index cancer diagnosis or during the study period. Patients were diagnosed between Jan 1, 2012, and Dec 31, 2017, with some variability in study periods between jurisdictions reflecting data availability. A federated or distributed analysis model was used, whereby standardised patient-level datasets were first prespecified, and then created and quality-assured in participating analytical hubs in each jurisdiction.[16,17] This step included the assessment of probable sources of bias, and checks on the distribution of key variables, helping to identify and correct occasional coding errors or misspecifications in jurisdictional datasets. Jurisdictional team coauthors identified potential quality problems in local data. Data were subsequently analysed within each hub, by means of centrally developed R Markdown code. Aggregate, group-level data suitable for publication were subsequently shared with the central team, without the transfer of patient-level data. Data were checked further for internal consistency during collation, tabulation, and meta-analysis; any queries raised were discussed with jurisdictional teams and resolved.

We examined the use of radiotherapy, defined as at least one administration (fraction) of radiotherapy from 31 days before to 365 days after the date of diagnosis in the cancer registry record; and time to first radiotherapy treatment (from diagnosis date) during the same period. Including a month of observation before the registered diagnosis date allows for the inclusion of neo-adjuvant radiotherapy initiated before the final histological diagnosis. All patients were followed-up for up to 1 year post-diagnosis or death if it occurred earlier, according to standard practice used by participating cancer registries.

The diagnosis date for each patient was assigned by participating registries following standard practices.[18–20] Generally, the recorded diagnosis dates precede or coincide with the start of treatment but occasionally, asynchronous data flows mean that treatment information is not available when the tumour is initially registered, on the basis of the date of histological verification, but made available subsequently. In such instances, when the tumour record is completed, the first treatment date might precede the registered diagnosis date by a few days. Therefore, to avoid underestimating radiotherapy use, we have included patients with diagnosis-to-radiotherapy intervals of up to −31 days.[21] Across all jurisdictions this group related to fewer than 5% of all cases.

Jurisdiction-level data, in the form of percentages or odds ratios (ORs) for radiotherapy use, and in the number of days or coefficients for time to first radiotherapy treatment, were available for all patients, and by age group, sex (or gender [depending on registry]; ie, male or female, from information in the cancer registry records), and diagnosis year, across all cancer sites and for each cancer site individually. Information was also available on stage at diagnosis (typically TNM stage), although availability and completeness varied by jurisdiction and cancer type (appendix p 6). The approach to selecting exposure variables was guided by feasibility and data availability across the jurisdictions. For example, no similar information was available on comorbidity or performance status, or treatment intent (neo-adjuvant–adjuvant, curative, or palliative).

Analysis

Random effects meta-analysis characterised inter-jurisdictional variation, through a direct central estimate of the outcome of interest and the calculation of 95% prediction intervals (95% PIs), which denote the range of outcomes we would expect to observe in similar jurisdictions not included in the analysis. Additionally, tau values (representing the SD) are reported as direct measures of the magnitude of interjurisdictional variability. Given the participating jurisdictions, results are likely to be applicable to jurisdictions with high Human Development Index values and universal health-care coverage, but not other settings.

We did not attempt to formally identify high or low radiotherapy use jurisdictions, because (1) there is no global consensus about the optimal amounts of radiotherapy use in a population, and such amounts cannot be inferred confidently without information on the use of other treatment methods, and a range of tumour and patient characteristics; (2) potential small differences in radiotherapy use ascertainment might lead to large differences between specific jurisdictions while having minimal effect on overall interjurisdictional variation; and (3) the sample of jurisdictions is small, therefore, it cannot be assumed that the observed value ranges between the participating jurisdictions represent the range across all high-income jurisdictions with universal health care coverage.

For radiotherapy use, meta-analyses encompassed the percentage of patients treated with radiotherapy, both for all eight cancer sites considered together, and each site separately, using the observed values, without casemix adjustment; and the ORs of radiotherapy use by sex (female compared with male), and by age group (15–64 years, 75–84 years, and 85–99 years compared with 65–74 years [the most common age group in our analysis sample]), adjusted for sex, age group, cancer site, and diagnosis year. We used categorical groupings of age to aid interpretation and simplify the federated analysis. There were no missing data in the analysis sample for age group, sex, cancer site, and diagnosis year, although information for stage at diagnosis was incomplete for 17·4% (137 167) of patients in the analysis sample. Therefore, the primary analysis did not adjust for stage at diagnosis, but results for stage-adjusted ORs of radiotherapy use by patient group were also presented

for jurisdictions with high stage completeness (>70%) for every individual cancer site. We have additionally examined radiotherapy use in patients with stage 2–3 rectal cancer, as rectal cancer had high completeness of information on stage and indications for radiotherapy use in this patient group have long been established. No information was collected on patients' race or ethnicity.

For time to first radiotherapy, meta-analyses primarily considered the median time to first radiotherapy treatment (from diagnosis date), for all eight cancer sites considered together, and each site separately by use of the observed values, without casemix adjustment; and differences in median time to first radiotherapy treatment by sex, and by age group, adjusted for sex, age (reference groups as above), cancer site, and diagnosis year.

Meta-analysis of the overall percentage of patients treated with radiotherapy assessed the log-odds of such treatment, which were then back-transformed to the percentage scale. Meta-analyses of adjusted odds ratios of radiotherapy use by patient group (from logistic regression) and of patient group differences in median time to first radiotherapy treatment (from quantile regression) used the model coefficients and standard errors reported by each jurisdiction, from regression models, specified by the central team. For radiotherapy use, meta-analyses were fit via restricted maximum likelihood by use of the R package metafor (version 3.4-0).[22] For median time to radiotherapy, meta-analysis was done by means of the quantile estimation method,[23] implemented in the R package metamedian (version 1.0.0). Additional analytical software information is included in the appendix (p 7).

We compared observed radiotherapy use against estimated population health need for radiotherapy by cancer site, on the basis of estimates arising from evidence-based indications, or comparative epidemiological data.

Estimates were not available because of small numbers for Prince Edward Island (for liver, pancreatic, and ovarian cancer) and Saskatchewan (ovarian cancer). These jurisdiction cancer-site strata (and associated all-site-combined strata) were excluded from meta-analyses of overall use and overall time to radiotherapy but included in those examining variation by age and sex.

Supplementary analysis examined the potential effect of differences in the age and cancer site composition of jurisdictional samples, fitting one-stage individual participant data meta-analysis models to the aggregate treatment use data (appendix p 8).

Primary data used in the study were collected under jurisdiction-specific regulations enabling cancer registration and the collection of administrative data on hospital admissions or treatments. No participant consent was applicable. No identifiable data were shared for this project. In England, Northern Ireland, Scotland, Wales, British Columbia, New Brunswick, Newfoundland &

	All jurisdictions (N=786 955)	Norway (N=37 185)	UK				Canada								Australia		
			England (N=373 194)	Northern Ireland (N=12 429)	Scotland (N=45 027)	Wales (N=26 139)	AB (N=25 093)	BC (N=40 064)	MB (N=9957)	NB (N=8135)	NL (N=6160)	NS (N=10 130)	ON (N=92 447)	PE (N=1365)	SK (N=8220)	NSW (N=53 198)	VIC (N=38 212)
Oesophageal	42 867 (5·4%)	1089 (2·9%)	27 274 (7·3%)	786 (6·3%)	3377 (7·5%)	1703 (6·5%)	889 (3·5%)	1398 (3·5%)	286 (2·9%)	204 (2·5%)	141 (2·3%)	377 (3·7%)	3099 (3·4%)	50 (3·7%)	224 (2·7%)	1970 (3·7%)	1576 (4·1%)
Stomach	44 281 (5·6%)	1884 (5·1%)	19 813 (5·3%)	805 (6·5%)	2337 (5·2%)	1656 (6·3%)	1293 (5·2%)	1934 (4·8 %)	528 (5·3%)	444 (5·5%)	398 (6·5%)	428 (4·2%)	6465 (7·0%)	70 (5·1%)	450 (5·5%)	3179 (6·0%)	2597 (6·8%)
Colon	200 252 (25·4%)	12 091 (32·5%)	88 219 (23·6%)	3122 (25·1%)	9599 (21·3%)	6142 (23·5%)	6403 (25·5%)	10 501 (26·2%)	2445 (24·6%)	1989 (24·4%)	2077 (33·7%)	2541 (25·1%)	24 481 (26·5%)	399 (29·2%)	2180 (26·5%)	16 316 (30·7%)	11 747 (30·7%)
Rectal	74 155 (9·4%)	4556 (12·3%)	33 905 (9·1%)	1107 (8·9%)	3535 (7·9%)	2577 (9·9%)	2486 (9·9%)	3913 (9·8%)	1108 (11·1%)	652 (8·0%)	632 (10·3%)	1000 (9·9%)	7845 (8·5%)	123 (9·0%)	819 (10·0%)	5459 (10·3%)	4438 (11·6%)
Liver	37 413 (4·8%)	972 (2·6%)	17 699 (4·7%)	450 (3·6%)	2340 (5·2%)	1155 (4·4%)	1333 (5·3%)	2377 (5·9%)	395 (4·0%)	243 (3·0%)	206 (3·3%)	365 (3·6%)	4129 (4·5%)	NA	271 (3·3%)	3155 (5·9%)	2323 (6·1%)
Pancreatic	62 031 (7·9%)	2945 (7·9%)	30 442 (8·2%)	904 (7·3%)	3054 (6·8%)	1965 (7·5%)	2114 (8·4%)	3286 (8·2%)	833 (8·4%)	616 (7·6%)	289 (4·7%)	698 (6·9%)	6456 (7·0%)	101 (7·4%)	658 (8·0%)	4498 (8·5%)	3172 (8·3%)
Lung	283 773 (36·1%)	11 547 (31·1%)	135 396 (36·3%)	4594 (37·0%)	18 662 (41·4%)	9365 (35·8%)	9408 (37·5%)	14 739 (36·8%)	3920 (39·4%)	3698 (45·5%)	2197 (35·7%)	4340 (42·8%)	35 092 (38·0%)	622 (45·6%)	3239 (39·4%)	16 334 (30·7%)	10 620 (27·8%)
Ovarian	40 607 (5·2%)	2101 (5·7%)	20 446 (5·5%)	661 (5·3%)	2123 (4·7%)	1576 (6·0%)	1167 (4·7%)	1916 (4·8%)	442 (4·4%)	289 (3·6%)	220 (3·6%)	381 (3·8%)	4880 (5·3%)	NA	379 (4·6%)	2287 (4·3%)	1739 (4·6%)

Data are n (%). AB=Alberta. BC=British Columbia. MB=Manitoba. NL=Newfoundland & Labrador. NS=Nova Scotia. ON=Ontario. PE=Prince Edward Island. SK=Saskatchewan. NSW=New South Wales. VIC=Victoria. NA=not available.

Table 1: **Analysis sample composition by jurisdiction and cancer site**

Labrador, and Prince Edward Island, no additional approvals were necessary given the nature of the study and its alignment with the routine surveillance function of cancer registries. In Ontario, Research Ethics Board approval was obtained by the University of Toronto Research Ethics Board. In Alberta, Health Research Ethics Board (Cancer Committee) Approval was obtained by the Alberta Health Services (CC-16-0868). In Manitoba, this study was approved by the University of Manitoba's Health Research Ethics Board and CancerCare Manitoba's Research and Resource Impact Committee (HS24284 [H2020:416]). In Nova Scotia, the study was endorsed by the Nova Scotia Health Research Ethics Board (Research Ethics Board file number: 1022055). In Norway, the Norwegian Regional Ethics Committee concluded that no approval was needed for this study (reference 2017/428REK sør-øst A), thus giving the authors exemption from the statutory duty of confidentiality; approval for handling indirect identifiable data was obtained from the Data Protection Officer of Oslo University Hospital (reference 2017/6597). In New South Wales, approval for linkage of the underlying data was granted by the NSW Population and Health Services Research Ethics Committee (HREC–15–CIPHS–15) and the Australian Institute of Health and Welfare Ethics Committee (EO2016–1–224). In Saskatchewan, approval was obtained from the University of Saskatchewan Research Ethics Board. In Victoria, approval for the data linkage and use of the Victorian data to study patterns of care was granted by the Cancer Council Victoria's Human Research Ethics Committee (HREC number 1312 and HREC number 1412).

Role of the funding source

The funders of the study facilitated resources for data collection and data analysis, but had no role in study design, data analysis, data interpretation, or the writing of the report.

Results

Between Jan 1, 2012, and Dec 31, 2017, there were 902 312 patients with a new diagnosis of one of the studied cancers, of whom 115 357 (12·8%) did not meet inclusion criteria, and 786 955 were included in the analysis. Sample compositions by cancer site, age group, and sex were broadly similar between the jurisdictions (table 1; appendix pp 9–10).

There was large variation in radiotherapy use by cancer site, with higher use in patients with oesophageal, rectal, lung, and stomach cancers, and infrequent (<6%) use in patients with pancreatic, liver, colon, and ovarian cancer

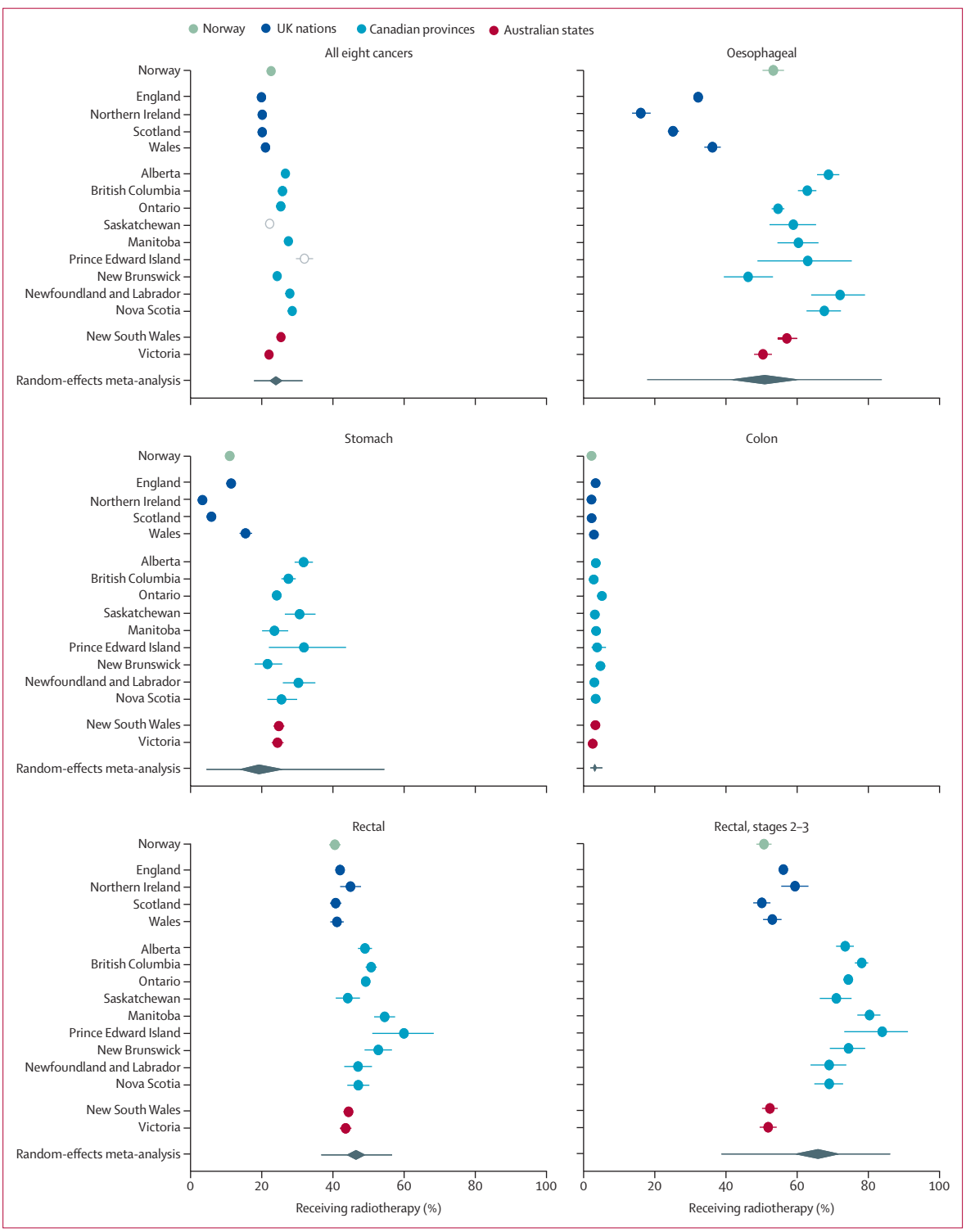
	Percentage of patients treated*						Odds ratio for patient group differences in radiotherapy use†					
	Pooled estimate	95% CI	95% PI‡	Tau log-odds scale§	I^2¶	Observed jurisdictional range	Pooled estimate	95% CI	95% PI‡	Tau log-odds scale§	I^2¶	Observed jurisdictional range
Site												
All	23·8%	22·2–25·5	17·5–31·5	0·174	99·6	19·7–28·5	..	..	..	..	..	..
Oesophageal	50·2%	41·5–58·8	17·8–82·4	0·703	99·5	16·0–70·9	1·39	1·05–1·86	0·40–4·86	0·571	99·1	0·28–2·73
Stomach	19·0%	14·1–25·2	4·6–53·6	0·727	99·4	3·5–31·4	0·33	0·24–0·46	0·08–1·38	0·647	99·2	0·06–0·88
Colon	2·9%	2·5–3·3	1·6–5·0	0·262	95·4	2·0–4·8	0·04	0·03–0·05	0·02–0·09	0·351	97·1	0·02–0·08
Rectal	45·2%	42·8–47·5	35·5–55·2	0·184	96·9	39·3–58·5	1·12	0·99–1·26	0·66–1·88	0·238	97·5	0·71–1·71
Rectal stage 2–3	64·2%	58·2–69·9	37·0–84·6	0·511	99·1	48·4–82·4	..	..	..	..	..	..
Liver	4·5%	3·6–5·7	1·8–11·2	0·441	94·8	2·0–9·2	0·06	0·05–0·08	0·03–0·15	0·375	92·7	0·03–0·15
Pancreatic	5·5%	4·2–7·2	1·7–16·5	0·553	98·3	2·0–12·3	0·08	0·06–0·11	0·02–0·28	0·554	98·1	0·02–0·21
Lung	40·6%	37·7–43·6	28·6–54·0	0·246	99·5	32·4–50·3	1**	ref	ref	ref	ref	ref
Ovarian	2·5%	1·9–3·3	0·8–7·6	0·520	93·5	1·1–6·6	0·03	0·03–0·05	0·01–0·10	0·465	91·2	0·01–0·09
Sex‖												
Male	26·2%	24·2–28·2	18·8–35·2	0·191	99·4	21·0–32·6	1	ref	ref	ref	ref	ref
Female	20·7%	19·3–22·2	15·4–27·2	0·160	98·9	17·3–24·6	0·88	0·85–0·92	0·77–1·01	0·060	82·4	0·74–1·02
Age												
15–64 years	27·9%	26·5–29·5	22·2–34·6	0·139	98·1	24·1–33·2	1·28	1·22–1·33	1·09–1·50	0·073	82·6	0·92–1·52
65–74 years	26·2%	24·6–27·8	20·1–33·3	0·154	98·4	22·0–30·8	1	ref	ref	ref	ref	ref
75–84 years	20·9%	19·2–22·6	14·6–28·8	0·193	98·6	16·0–25·9	0·76	0·72–0·79	0·62–0·91	0·086	85·6	0·65–0·90
85–99 years	11·4%	9·7–13·4	5·7–21·5	0·339	98·4	6·2–20·1	0·38	0·33–0·45	0·20–0·73	0·295	96·6	0·23–0·81

PI=prediction interval. *Meta-analysis summaries of the percentage of patients treated with radiotherapy, overall and by cancer site, sex, and age group. Results are not adjusted for sex, age (in years), cancer site, or any other variable. †Meta-analysis summaries for patient group differences in radiotherapy use. Results are mutually adjusted for all variables shown (sex, age group, and cancer site) and diagnosis year. ‡PIs show the range that 95% of new jurisdictions are expected to fall into and incorporates both the uncertainty around the overall average and the spread of the included jurisdictions. §The estimated SD of the included jurisdictional estimates, directly measuring the spread of jurisdictions. ¶The proportion of total variation not due to sampling variation. ‖Relates to biological sex in some registries, but gender at diagnosis of cancer in others. **Comparisons against lung cancer are used as a means of indirectly considering the consistency of patterns of variation in radiotherapy use between different cancer sites across the jurisdictions.

Table 2: **Meta-analysis summaries of patients treated with radiotherapy**

(table 2). Patterns of cancer site variation were consistent between jurisdictions, but with large interjurisdictional variations in cancer-site-specific use, as indicated by wide 95% PIs (figure 1, table 2, appendix pp 11–12).

Specifically, 95% PIs were 17·8–82·4 (pooled estimate 50·2%) for oesophageal, 35·5–55·2 (45·2%) for rectal, 28·6–54·0 (40·6%) for lung, and 4·6–53·6 (19·0%) for stomach cancer. As indicated by corresponding



(Figure 1 continues on next page)

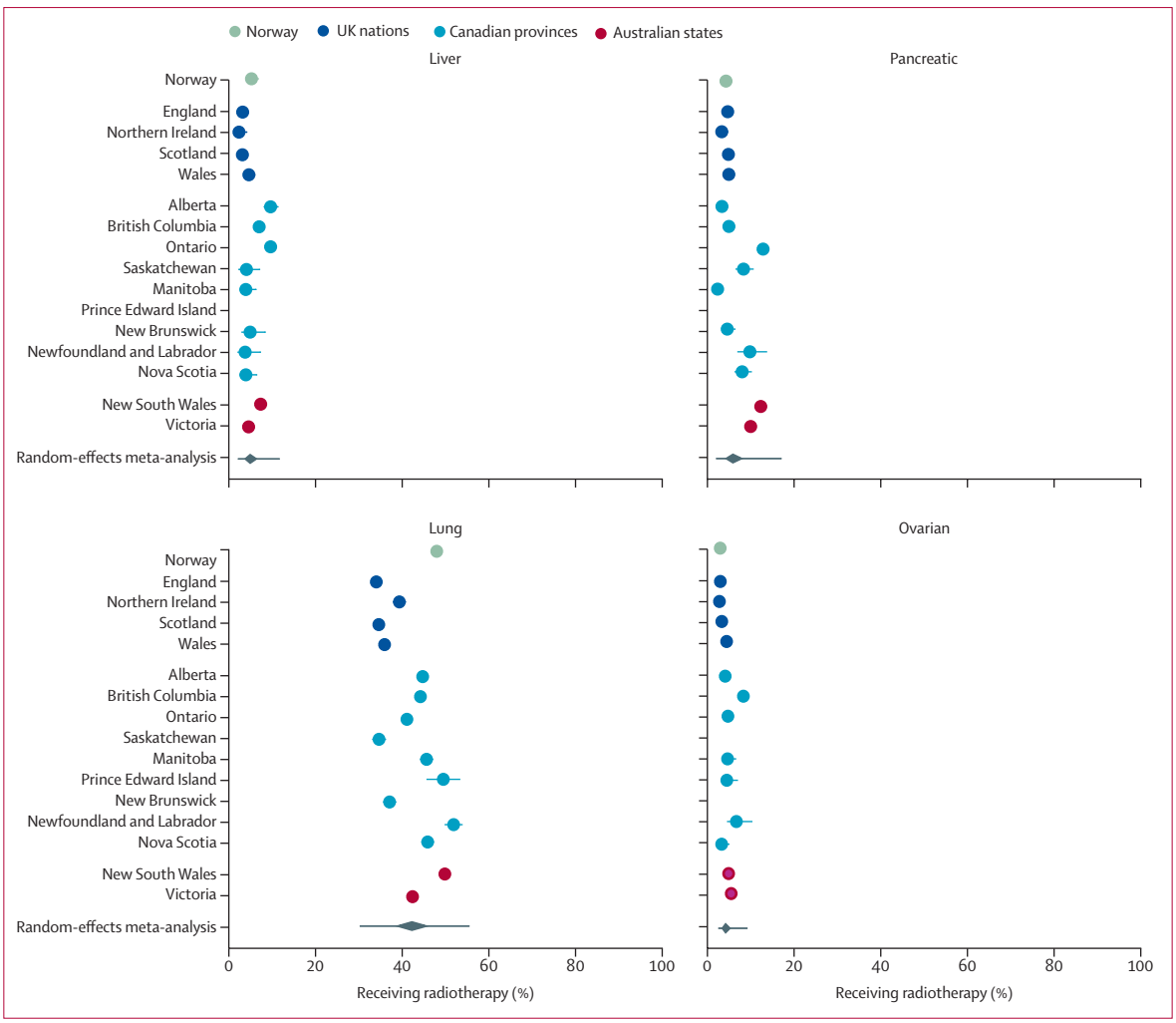


Figure 1: **Overall crude proportion of patients treated with radiotherapy in each jurisdiction, by cancer site**
Circles show proportions, and lines show the associated 95% CIs. Grey diamonds show the meta-analysis estimates, and the width of the diamonds shows the related 95% CIs; the wider grey lines show the associated 95% prediction intervals. Site-specific jurisdictional estimates not included in producing relevant meta-analysis estimates are shown as hollow light grey circles (relates to Prince Edward Island estimates for liver, pancreatic, and ovarian cancer and Saskatchewan estimates for ovarian cancer; for this reason, additionally, no all-eight cancer site estimates for these jurisdictions are reported, please see main text, Methods). For the stage 2–3 rectal cancer analysis, regional stage categories were used in New South Wales and Norway (appendix pp 11–12).

tau values, interjurisdictional variation was largest for stomach (0·727) and oesophageal (0·703) cancer, and smallest for rectal (0·184) and lung (0·246) cancer (table 2). For patients with stage 2–3 rectal cancer, interjurisdictional variation was larger than that observed for all patients with rectal cancer (95% PI 37·0–84·6; pooled estimate 64·2%, table 2; figure 1). Interjurisdictional variation was also substantial for the four sites with infrequent radiotherapy use, with 95% PIs of 1·7–16·5% for pancreatic, 1·8–11·2% for liver, 1·6–5·0% for colon, and 0·8–7·6% for ovarian cancer. Typically, 95% PIs were similar to the observed jurisdictional ranges, although slightly wider (table 2). Use of radiotherapy was stable during the study period across all studied cancer sites (appendix p 13).

Among the 172 331 patients who received radiotherapy, after adjustment for age group, cancer site and diagnosis year, a small sex difference was observed, with females having lower radiotherapy use than males, with some variation across jurisdictions (OR 0·88, 95% PI 0·77 to 1·01; table 2; figure 2). Patients aged 85–99 years had around three-times lower odds of receiving radiotherapy than those aged 64–74 years (OR 0·38; table 2); these age differences varied substantially between the jurisdictions (95% PI 0·20 to 0·73; table 2; figure 2). Adjustment for stage made little difference to the findings of variation by sex or age group (figure 2—hollow circles).

The pooled estimate of the median time to first radiotherapy varied substantially by cancer site, with relatively short medians for lung (49·2 days), rectal (56·0 days), and oesophageal cancer (62·0 days), and relatively long medians for colon (96·1 days), pancreatic

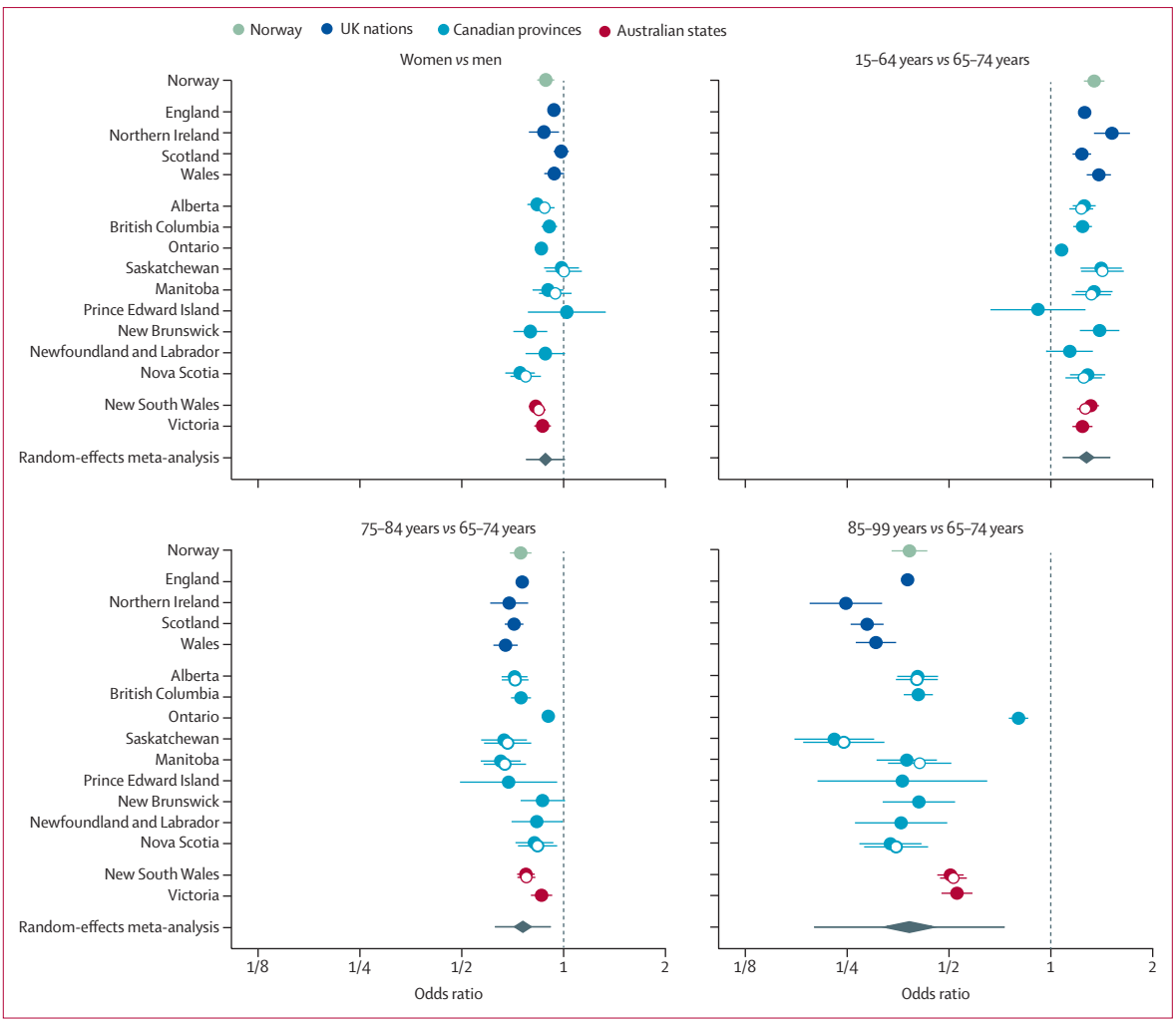


Figure 2: **Variation in use of radiotherapy by sex and age group, by jurisdiction**
Results are mutually adjusted for all variables shown (sex, age group, and cancer site) and diagnosis year. Circles show jurisdictional odds ratios, and lines show the associated 95% CIs. Grey diamonds show the meta-analysis estimates; the width of the diamonds shows the related 95% CIs; wider grey lines show the associated 95% prediction intervals. White circle estimates are adjusted for stage at diagnosis; only shown for jurisdictions with more than 70% completeness of information on stage at diagnosis for every cancer site. These adjust for stage categories used by the jurisdiction including a missing stage indicator (TNM 1, 2, 3, 4, and missing, except for New South Wales where the categories were localised, regional [in adjacent organs], regional [in lymph nodes], distant, and missing; appendix pp 11–12).

(119·9 days), and ovarian cancer (169·9 days; table 3; figure 3; appendix p 14). Cancer sites with low radiotherapy use tended to have longer median time-to-first-radiotherapy intervals (appendix p 15). Variation by cancer site was overall consistent between the jurisdictions, but with substantial interjurisdictional variability for each cancer site (eg, oesophageal cancer 95% PI 11·3–112·8 days; rectal cancer 95% PI 34·7–77·3 days; table 3). As denoted by the respective tau values, interjurisdictional variation was largest for pancreatic, ovarian, and liver cancer (table 3; figure 3), and smallest for rectal, lung, and stomach cancer.

There were minimal differences in time to first radiotherapy treatment by sex, consistently between jurisdictions (table 3; appendix p 16). The oldest patients (85–99 year group) had slightly shorter intervals (–9·5 days in patients aged 85–99 years *vs* 65–74 years, 95% PI –26·4 to 7·4) with interjurisdictional variability in both direction and size (table 3; appendix p 16).

Considering jurisdictional patterns, typically, Canadian jurisdictions had higher use and UK jurisdictions lower use than the average jurisdiction, with some variability by cancer site (figure 1; appendix pp 17–18). The two Australian jurisdictions had similar use to Canadian jurisdictions for oesophageal, stomach, and lung cancer, but similar to UK jurisdictions for rectal cancer. Norway had similar use patterns to Australian and Canadian jurisdictions for oesophageal and lung cancer, but similar to UK jurisdictions for stomach and rectal cancer. The decrease in radiotherapy use with increasing age group was steeper in three of the UK nations and Saskatchewan, and less steep in Ontario and the two Australian jurisdictions (figure 2). There was no consistent pattern

	Median time to treatment*						Difference in median time to treatment by patient group†					
	Pooled estimate, days	95% CI	95% PI‡	Tau natural scale, days§	I^2¶	Observed jurisdictional range	Pooled estimate, days	95% CI	95% PI‡	Tau natural scale, days§	I^2¶	Observed jurisdictional range
Site												
All	54·7	48·3 to 61·2	27·5 to 81·9	12·3	99·7	42·0 to 81·0	..	..	..	..	..	..
Oesophageal	62·0	50·6 to 73·5	11·3 to 112·8	23·2	99·6	36·5 to 108·0	12·4	4·9 to 19·9	−20·4 to 45·2	15·0	98·7	−6·0 to 52·0
Stomach	68·9	61·8 to 76·1	40·1 to 97·7	13·1	91·5	52·0 to 105·5	18·8	15·1 to 22·6	6·6 to 31·0	5·4	65·0	6·0 to 66·3
Colon	96·1	85·0 to 107·2	52·3 to 139·9	19·9	90·7	60·0 to 149·0	43·7	32·5 to 55·0	0·0 to 87·5	19·8	92·4	16·0 to 93·0
Rectal	56·0	51·1 to 60·8	34·7 to 77·3	9·7	99·3	39·0 to 72·0	6·6	1·1 to 12·1	−17·5 to 30·7	11·0	98·8	−9·0 to 23·8
Liver	65·7	49·3 to 82·1	3·2 to 128·1	28·1	85·7	21·0 to 116·0	16·1	−3·2 to 35·4	−53·5 to 85·8	31·2	85·2	−26·0 to 71·3
Pancreatic	119·9	96·4 to 143·3	23·1 to 216·6	43·8	95·9	56·5 to 237·0	68·3	51·4 to 85·2	4·2 to 132·3	28·9	89·9	14·3 to 188·0
Lung	49·2	43·3 to 55·1	22·9 to 75·5	12·0	99·4	35·0 to 78·0	0‖	ref	ref	ref	ref	ref
Ovarian	169·9	147·6 to 192·2	91·6 to 248·2	34·7	83·7	83·0 to 242·5	113·4	97·4 to 129·3	67·6 to 159·2	19·9	64·6	27·0 to 202·0
Sex												
Male	..	..	..	..	..	..	0	ref	ref	ref	ref	ref
Female	..	..	..	..	..	..	1·2	0·6 to 1·7	0·6 to 1·8	0·0	0·0	−2·0 to 5·0
Age												
15–64 years	..	..	..	..	..	..	−1·9	−3·3 to −0·4	−7·0 to 3·2	2·3	71·0	−8·0 to 3·0
65–74 years	..	..	..	..	..	..	0	ref	ref	ref	ref	ref
75–84 years	..	..	..	..	..	..	−2·9	−5·2 to −0·6	−11·8 to 6·1	4·1	87·8	−12·3 to 3·8
85–99 years	..	..	..	..	..	..	−9·5	−13·7 to −5·3	−26·4 to 7·4	7·7	92·5	−27·0 to 7·0

PI=prediction interval. *Meta-analysis summaries for time to first radiotherapy, overall and by cancer site (method by McGrath and colleagues[21]). Results are not adjusted for sex, age, cancer site, or any other variable. †Meta-analysis summary for differences in median time to radiotherapy in patients who received radiotherapy by sex, age group, and cancer site. Results are mutually adjusted for all variables shown (sex, age group, and cancer site) and diagnosis year. ‡PIs show the range that 95% of new jurisdictions are expected to fall into and incorporates both the uncertainty around the overall median and the spread of the included jurisdictions. Negative values at the lower bound of the 95% PI can occur because, according to our definition, radiotherapy could have been administered from −31 days to +365 from the recorded date of diagnosis by the cancer registry. The inclusion of the −31 day interval before diagnosis allows for instances where a patient is treated with radiotherapy after a clinical diagnosis but before the date of cancer registration. §The estimated SD of the included jurisdictional estimates, directly measuring the spread of jurisdictions. ¶The proportion of total variation not due to sampling variation. ||Comparisons against lung cancer are used as a means of indirectly considering the consistency of patterns of variation in radiotherapy use between different cancer sites across the jurisdictions.

Table 3: **Meta-analysis summaries for time to first radiotherapy**

of interjurisdictional variation in time to first radiotherapy, or in sex and age group differences in either use or time to radiotherapy (figure 3; appendix pp 14, 16).

Comparisons of the observed radiotherapy use against theoretical health need indicated that although use was broadly consistent with estimated theoretical need in the average jurisdiction, many jurisdictions had lower than expected use (appendix pp 17–18).

In the supplementary analysis exploring compositional differences in jurisdictional analysis samples, adjustment for cancer site or age made little difference to the estimated interjurisdictional variation, as evidenced by comparisons of the tau statistic. Additional results and information on morphology type distributions in participating countries are provided in the appendix (pp 19–51).

Discussion

We used population-based data from 16 international jurisdictions with similar health systems to characterise interjurisdictional variation in use and time to radiotherapy in patients with cancers of eight different organs. Patterns of variation in radiotherapy use by cancer site were consistent across the jurisdictions, although with large cancer-specific interjurisdictional differences. Patterns of variation between included Australian, Canadian, and European jurisdictions were also apparent. Older patients were less likely to be treated with radiotherapy, with substantial interjurisdictional variation in these age differences, particularly among the oldest patients. There was large variation in time to first radiotherapy treatment by cancer site, with substantial interjurisdictional variability for each cancer site. There were small age differences in time to first radiotherapy treatment with interjurisdictional variability in both direction and size.

To our knowledge, this study establishes for the first time the frequency of radiotherapy use, alongside time to radiotherapy initiation, in patients diagnosed in the last decade with eight common cancers in international jurisdictions from three continents. Relevant international variation evidence thus far typically relates to fewer cancer sites and European countries, without considering treatment timeliness.[9,10] The infrequent use of radiotherapy in patients with colon, liver, pancreatic, and ovarian cancer concords with clinical practice guidelines. The observed age inequalities in radiotherapy use are consistent with previous evidence, which did not however quantify how the strength of such age inequalities varies between jurisdictions.[3,4,24] Compared

Figure 3: **Median time to radiotherapy for each jurisdiction, by cancer site**
Circles show medians and related lines show the IQRs. Grey diamonds show the meta-analysis estimates; the width of the diamonds shows the related 95% CIs; wider grey lines show the associated 95% prediction intervals. Highly uncertain estimates have been suppressed from visualisation but were included in the meta-analysis. Site-specific jurisdictional estimates not included in producing meta-analysis estimates are shown as light grey circles.

against theoretical radiotherapy need estimates in patients with the studied cancer sites, many jurisdictions had lower than expected use. The generally lower use of radiotherapy in the UK jurisdictions compared with those in Canada and Australia mirrors differences in radiotherapy health need estimates produced by UK, Canadian, and Australian authors, possibly reflecting differences in evidence interpretation and clinical protocols. The findings concord with previous evidence indicating that health needs for radiotherapy use are often not met, which highlights the need for examining radiotherapy use as a global issue in cancer control.[6–8]

Considering the limitations, as the latest study year was 2017, the findings might not represent current radiotherapy use in participating jurisdictions, given probable changes in radiotherapy indications (eg, for early-stage lung cancer) and in system capacity. Furthermore, the findings are not likely to be generalisable to jurisdictions in low-income and middle-income countries or countries with substantially different health systems to those of the studied jurisdictions.

It was not possible to examine information on use of other treatment modalities (surgery and chemotherapy) in combination with radiotherapy. However, it is worth noting that if the use of surgery and chemotherapy contributed to the interjurisdictional variation in radiotherapy use, their own use would also need to vary between jurisdictions. We had no information on treatment intent; stage at diagnosis could be used as a surrogate marker of curative or palliative intent, but its completeness was overall low and variable. Therefore, we have only performed stratified analysis by disease stage for rectal cancer where stage completeness was high and guideline recommendations supporting radiotherapy use were well-established. We had no information on whether radiotherapy regimens were completed. Hypofractionated regimens could help to increase capacity, thereby increasing radiotherapy use, but fractionation information was not available across the jurisdictions.

Regarding patient factors, comorbidity is known to be associated with radiotherapy use but is inconsistently coded in hospital data across the participating jurisdictions.[25] Large variation in morbidity status between the participating jurisdictions is however unlikely, given their overall similar demographic structures. Similarly, we had no information on patient performance status. Ethnic group and socioeconomic status information was not considered but approaches to measure them consistently across international jurisdictions are lacking.[26] There were no data on patient preference for and acceptability of radiotherapy. The findings regarding overall radiotherapy use and time to first radiotherapy treatment were not adjusted for age group, but analysis samples had broadly similar age composition; furthermore, supplementary analyses indicated that interjurisdictional variation in radiotherapy use seems to be independent of the age and cancer site casemix of the studied jurisdictional populations. Additionally, we did not want to adjust the observed overall use to avoid obscuring interjurisdictional variation in how patients are managed (eg, by age group), which we examined by means of meta-analysis.

Regarding health system organisational factors, the proportions of cancer patients residing in rural areas would vary between jurisdictions, and we had no information on distance between the patients' residence and closest radiotherapy centre, a factor associated with radiotherapy use.[27,28] All participating jurisdictions are served by health-care systems with universal coverage, enabling access to cancer treatment. Financial barriers in accessing radiotherapy are therefore unlikely sources of interjurisdictional variation.

We consider three hypotheses that can help interpret the findings. First, that observed variation is due to confounding. This hypothesis does not deny the presence of variation but might help to explain it, for example, if unmeasured confounder variables were unequally distributed across jurisdictional samples, or if their effect sizes varied interjurisdictionally. Given the large size of observed variations, distributional and effect size differences of confounder variables would need to be implausibly large to substantially affect the findings. It is, for example, unlikely that variation in the prevalence of morbidity between older patients differs substantially between jurisdictional populations, to the level needed to produce the large size of observed inter-jurisdictional variation in age differences. In principle, interjurisdictional variation in tumour morphology in patients with oesophageal, stomach, liver, lung, and ovarian cancer could contribute to variation in radiotherapy use, but morphology type distributions were similar among participating jurisdictions.

Second, that the observed variation is artefactual. For example, owing to differences in operational definitions and the completeness of ascertainment of radiotherapy use and its timing in different data sources. This hypothesis is hard to examine empirically currently, although we observe large differences between jurisdictions with established high-quality population-data sources. Furthermore, any potential undercounting of radiotherapy use is unlikely to vary by sex, age group, or cancer site, or to be influencing variation in time to radiotherapy among treated patients; therefore, these aspects of observed variations are particularly robust. Although we have used the best data sources for examining radiotherapy use in participating jurisdictions during the study period, future research should aim to develop and cross-validate operational definitions and the completeness of information on radiotherapy use. In only a few cases, we observed a negative time-to-treatment interval, probably reflecting instances in which tumour registration based on the date of histological verification has occurred before the treatment start date

was identified. Including these cases prevents biased estimation of true treatment use status.[21] Because such instances consistently related to only a few cases, the effect on the overall time-to-treatment distribution is small, and unlikely to substantially influence the observed interjurisdictional differences in median time to radiotherapy.[29]

Third, that the observed variation is real. Having considered alternative explanations, we conclude that in major part the observed variation is due to genuine interjurisdictional differences in radiotherapy use, not accounted by other factors. This is further corroborated by two observations. First, interjurisdictional variation in the use of radiotherapy overall (considering all eight cancer sites together) is relatively small, compared with variation for specific cancer sites such as oesophageal, stomach, rectal, and lung, pointing to variation in clinical practice for different sites. Second, stratified analysis revealed prevailing variability in radiotherapy use in patients with stage 2–3 rectal cancer, a patient group with well-established indication for radiotherapy, and for which we would have expected jurisdictional variation to be rare, although the opposite is observed.

It is not possible from our data to infer the probable causes of such real variation. Differences in the content of clinical guidelines in different health systems, or their implementation, or both; capacity constraints in facilities and the availability of trained health-care professionals; variation in professional culture and norms towards more or less conservative management, as well as patient treatment preferences, variable differences in clinical practice between providers or hospital teams within the same country, the geographical location of radiotherapy centres in relation to population residence; variable research infrastructure that could enable access to clinical trials; and differences in the availability and content of national cancer control strategies might all be contributing to interjurisdictional differences in radiotherapy use.[14,15,30] The examination of these factors will require further studies, including both epidemiological and mixed methods research.

In our study, artefactual causes of interjurisdictional variation in time to radiotherapy are unlikely among patients identified as having been treated with radiotherapy. Interjurisdictional differences in the promptness of staging investigations, the stage at diagnosis and the use of neo-adjuvant regimens (particularly for rectal cancer) might be contributing to variation in treatment timeliness.[15]

In conclusion, large variation in both the frequency of radiotherapy use in the year post-diagnosis, and time to first radiotherapy treatment is observed across included high-income countries, indicating variations in health system propensity for radiotherapy use. Use of radiotherapy varied by age group, and age group differences varied in size between jurisdictions. The findings underline the value of international studies to understand variation in practice between different health systems. To support efforts to improve care delivery, the reasons for such variations need to be established, and their probable contribution to interjurisdictional survival differences estimated in future studies.

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Declaration of interests
MEB reports personal fees from GRAIL Bio UK Ltd, for Independent Data Monitoring Committee (IDMC) membership unrelated to this study. OB and GM report salary compensation for analysis of trial data in preparation for review by the Data Safety Monitoring Board for the POWERRANGER trial (NCT01404156), unrelated to this project. DWH reports grant support by Moondance Cancer Initiative (to institution) in relation to exploring bowel cancer audit data. YN reports grant support to The Cancer Registry of Norway by the Norwegian Cancer Society on standardised cancer pathways (no direct payment). RRW reports research grant funding by the Michael Smith Foundation for Health Research, the First Nations Health Authority/Canadian Partnership Against Cancer, and the BC Cancer Foundation for unrelated to the present study public health research projects. GL declares research grant funding by the study sponsors to his employer (University College London).

Data sharing
Most of the aggregate data are shared in the main text or the appendix, and all R code and aggregate data used for meta-analyses are available on GitHub (https://github.com/MattEBarclay/icbp_radio_sharing). The following analytical resources are available from the authors

(1) a Microsoft Excel spreadsheet describing the analysis dataset structure (data items and properties), exemplified for a jurisdiction; (2) a write-out of SQL code (in Microsoft Word) that can be used (adapted) to generate analysis-ready datasets; (3) an R markdown quality assurance code for analysis datasets; (4) an R markdown output of quality assurance of analysis dataset for an exemplar jurisdiction; and (5) an R markdown analysis code designed to be run against analysis datasets and produce aggregate data outputs in comma-separated value files. Primary data used in this study can be requested following the data access policies of data owner organisations (Cancer Registry of Norway; National Disease Registration Service, NHS England; Northern Ireland Cancer Registry; Scottish Cancer Registry, Public Health Scotland; Welsh Cancer Intelligence and Surveillance Unit, Public Health Wales; Alberta Cancer Registry, Cancer Care Alberta, Alberta Health Services; British Columbia Cancer Registry, BC; Manitoba Cancer Registry, CancerCare Manitoba; New Brunswick Provincial Cancer Registry, New Brunswick; Provincial Cancer Care Program, NL; Nova Scotia Cancer Registry; Ontario Health (Cancer Care Ontario); Prince Edward Island Cancer Registry; Saskatchewan Cancer Agency; NSW Cancer Registry, Cancer Institute NSW; Victorian Cancer Registry). Additionally, for Ontario, Ontario Health is prohibited from making the data used in this research publicly accessible if it includes potentially identifiable personal health information or personal information as defined in Ontario law, specifically the Personal Health Information Protection Act and the Freedom of Information and Protection of Privacy Act. On request, data de-identified to a level suitable for public release can be provided.

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