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Reporting Summary

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☒	☐	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Python 3.9, https://github.com/juangamella/aicp.git
Data analysis	Python 3.9, PyTorch 1.10, https://github.com/CTPLab/AutoCI.git, https://github.com/juangamella/aicp.git

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The PORTEC dataset analysed in this study are not publicly available due to restrictions by privacy laws. The dataset and tumour material are currently available to the members of the international TransPORTEC consortium, and the consortium is open for requests for sharing of the data and material after receipt and evaluation of a scientific proposal. Requests should be addressed to the corresponding author. Please contact Dr. Horeweg via n.horeweg@lumc.nl for more details. Depending on the specific research proposal, the TransPORTEC consortium will determine when, for how long, for which specific purposes, and under which conditions the requested data can be made available, subject to ethical consent. The code used to generate the data of the toy experiments is available via the link https://github.com/juangamella/aicp.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The PORTEC 1 (Creutzberg et al., 2000) and 2 (Nout et al., 2010) trials recruited 714 (since 1990 - 1997) and 427 (since 2000 - 2006) patients with early stage endometrial carcinoma respectively. Note: Our work is a secondary causal analysis on existing PORTEC 1 and 2 clinical trials. For more details about the clinical trials, see also Creutzberg, Carien L., et al. "Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial." The Lancet 355.9213 (2000): 1404-1411. Nout, R. A., et al. "Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial." The Lancet 375.9717 (2010): 816-823.
Data exclusions	In our study, 305 cases from PORTEC 1 (42.7%) and 335 cases from PORTEC 2 (78.5%) with complete clinicopathological datasets were aligned and used in the experiments.
Replication	In our study, to verify the experimental finds, we re-run the algorithmic codes multiple times with undetermined random seeds. Almost all the experiments presented clear causal variable differentiations. The minor failure cases are mainly due to the intrinsic randomness of the proposed algorithm.
Randomization	PORTEC 1: Patients with stage-1 endometrial carcinoma (grade 1 with deep [>=50%] myometrial invasion, grade 2 with any invasion, or grade 3 with superficial [<50%] invasion) were enrolled. Patients from 19 radiation oncology centres were randomised to pelvic radiotherapy (46 Gy) or no further treatment. Central blocked randomisation by telephone was done at the DDHCC trial office with variable block sizes and stratified by radiation oncology centre and depth of myometrial invasion (<50% vs >=50%). PORTEC 2: Patients with endometrial adenocarcinoma were eligible for the trial on the basis of the following features of high-intermediate risk: (1) age greater than 60 years and stage 1C grade 1 or 2 disease, or stage 1B grade 3 disease; and (2) stage 2A disease, any age (apart from grade 3 with greater than 50% myometrial invasion). Participants were assigned to either EBRT or VBT via internet with an application trial online process (TOP). Patient details and answers about eligibility questions were entered by the data managers of the participating centres, after which the treatment was allocated by TOP with a biased coin minimisation procedure, with stratification factors FIGO stage, radiotherapy centre, brachytherapy (low-dose vs high-dose rate), and patient age (<60 years vs >=60 years). For more details about the PORTEC clinical trials see Creutzberg et al., 2000 and Nout et al., 2010.
Blinding	The investigators were blinded to group allocation during data collection and/or analysis.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	PORTEC 1: Age <60: 201 (28%), 60-70: 270 (38%), >70: 243 (34%). Grade 1: 142 (41%), 2: 498 (70%), 3: 74 (10%). PORTEC 2: Age <60: 16 (4%), 60-70: 208 (49%), >70: 203 (47%). Grade 1: 202 (47%), 2: 191 (45%), 3: 34 (8%). See more population characteristics in Creutzberg et al., 2000 and Nout et al., 2010.
Recruitment	Note: Our work is a secondary causal analysis on existing PORTEC 1 and 2 clinical trials. For more details about the clinical trials, see also: Creutzberg, Carien L., et al. "Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial." The Lancet 355.9213 (2000): 1404-1411. Nout, R. A., et al. "Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediaterisk (PORTEC-2): an open-label, non-inferiority, randomised trial." The Lancet 375.9717 (2010): 816-823. PORTEC 1: All but one of the 20 radiation oncology centres in the Netherlands took part. The patients were evaluated and treated by their local gynaecologist, most often a general gynaecologist with special interest in gynaecological oncology. Initial evaluation included a pelvic examination, and endometrial curettage with separate endocervical and endometrial sampling. Preoperative evaluation included a medical history and physical and pelvic examination, chest radiography, complete blood count, and blood-chemistry tests. An abdominal computed-tomography scan was optional. At the time of surgery, a median laparotomy was done and, after obtaining a peritoneal cytology specimen, abdominal exploration with careful palpation and biopsy of any suspicious lymph nodes or lesions was done. A total abdominal hysterectomy and bilateral salpingo-oophorectomy was done, without routine lymphadenectomy. The diagnoses of endometrial carcinoma, of the histological grade, histological subtype, and depth of myometrial invasion were made by the regional pathologist. Vascular space invasion and perineural invasion were noted if present. FIGO 1988 staging30 was assigned on the basis of surgical and pathological findings. Women of any age with a histologically proven endometrial adenocarcinoma (also including adenocarcinoma with squamous features, adenocarcinoma not otherwise specified, adenosquamous carcinoma, papillary serous carcinoma, and clear-cell carcinoma), postoperative FIGO stage I, grade 1 with deep (>=50%) myometrial invasion, grade 2 with any invasion, or grade 3 with superficial (<50%) invasion were eligible for the study. While peritoneal cytology was recommended, patients were not excluded if this had not been done. All patients had a WHO-performance score of 0–2. Patients were excluded if they had a history of invasive cancer (except for basal cell carcinoma of the skin), and if they had previously received chemotherapy, hormonal therapy, or radiotherapy. The interval between surgery and radiotherapy had to be less than 8 weeks. Informed consent was obtained from all patients. PORTEC 2: The PORTEC-2 trial was a multicentre randomised trial, in which 19 of the 21 Dutch radiation oncology centres participated. The study was undertaken between May 27, 2002, and Sept 25, 2006. Patients were assessed and operated on by their regional gynaecologist. Initial assessment included pelvic examination and endometrial tissue biopsy. Preoperative assessment included chest radiography and haematology and chemistry tests. During surgery a peritoneal cytology specimen was obtained and abdominal exploration undertaken. Surgery consisted of total abdominal hysterectomy and bilateral salpingo-oophorectomy; clinically suspicious pelvic or periaortic lymph nodes were removed, but no routine lymphadenectomy was done. Diagnosis, typing, and grading of endometrial carcinoma was done by the regional pathologist. FIGO 1988 staging was assigned on the basis of surgical and pathological findings. Patients with endometrial adenocarcinoma were eligible for the trial on the basis of the following features of high-intermediate risk: (1) age greater than 60 years and stage 1C grade 1 or 2 disease, or stage 1B grade 3 disease; and (2) stage 2A disease, any age (apart from grade 3 with greater than 50% myometrial invasion). All patients had a WHO performance score of 0–2. Exclusion criteria were: serous or clear cell carcinoma; staging lymphadenectomy; interval between surgery and radiotherapy more than 8 weeks; history of previous malignant disease; previous radiotherapy, hormonal therapy, or chemotherapy; and previous diagnosis of Crohn's disease or ulcerative colitis.
Ethics oversight	The PORTEC study protocols were approved by the Dutch Cancer Society and by the medical ethics committees at participating centers. Both studies were conducted in accordance with the principles of the Declaration of Helsinki. All patients provided informed consent for study participation.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	PORTEC 1: Daniel Den Hoed Cancer Center Trial Office (DDHCC) PORTEC 2: NCT00376844

Study protocol	Note: Our work is a secondary causal analysis on existing PORTEC 1 and 2 clinical trials. See more protocol details in Creutzberg et al., 2000 and Nout et al., 2010.
Data collection	PORTEC 1: All but one of the 20 radiation oncology centres in the Netherlands took part in patient data collection during 1990 - 1007. PORTEC 2: 19 of the 21 Dutch radiation oncology centres in the Netherlands participated in the data collection and assessment since 2000-2006. See more data collection details in Creutzberg et al., 2000 and Nout et al., 2010.
Outcomes	PORTEC 1: 5-year actuarial locoregional recurrence rates were 4% in the radiotherapy group and 14% in the control group (p0.001). Actuarial 5-year overall survival rates were similar in the two groups: 81% (radiotherapy) and 85% (controls), p0.31. Endometrial-cancer-related death rates were 9% in the radiotherapy group and 6% in the control group (p=0.37). Treatment-related complications occurred in 25% of radiotherapy patients, and in 6% of the controls (p0.0001). Two-thirds of the complications were grade 1. Grade 3–4 complications were seen in eight patients, of which seven were in the radiotherapy group (2%). 2-year survival after vaginal recurrence was 79%, in contrast to 21% after pelvic recurrence or distant metastases. Survival after relapse was significantly (p0·02) better for patients in the control group. Multivariate analysis showed that for locoregional recurrence, radiotherapy and age below 60 years were significant favourable prognostic factors. PORTEC 2: At median follow-up of 45 months (range 18–78), three vaginal recurrences had been diagnosed after VBT and four after EBRT. Estimated 5-year rates of vaginal recurrence were 1.8% (95% CI 0.6-5.9) for VBT and 1.6% (0.5–4.9) for EBRT (hazard ratio [HR] 0.78, 95% CI 0.17–3.49; p=0.74). 5-year rates of locoregional relapse (vaginal or pelvic recurrence, or both) were 5.1% (2.8–9.6) for VBT and 2.1% (0.8–5.8) for EBRT (HR 2.08, 0.71–6.09; p=0.17). 1.5% (0.5-4.5) versus 0.5% (0.1-3.4) of patients presented with isolated pelvic recurrence (HR 3.10, 0.32–29.9; p=0.30), and rates of distant metastases were similar (8.3% [5.1–13.4] vs 5.7% [3.3–9.9]; HR 1.32, 0.63–2.74; p=0.46). We recorded no differences in overall (84.8% [95% CI 79.3–90.3] vs 79.6% [71.2–88.0]; HR 1.17, 0.69–1.98; p=0.57) or disease-free survival (82.7% [76.9–88.6] vs 78.1% [69.7–86.5]; HR 1.09, 0.66–1.78; p=0.74). Rates of acute grade 1–2 gastrointestinal toxicity were significantly lower in the VBT group than in the EBRT group at completion of radiotherapy (12.6% [27/215] vs 53.8% [112/208]). See more outcome details in Creutzberg et al., 2000 and Nout et al., 2010.