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Scientific Article

Risk of Bacterial, Viral, and Fungal Infections in Patients With Solid Malignant Tumors Treated With Curative Intent Radiation Therapy

Cynthia Terrones-Campos, MD,[a,*] Bruno Ledergerber, PhD,[a] Lena Specht, MD, DMSc,[b] Ivan Richter Vogelius, PhD, DMSc,[b] Marie Helleberg, MD, PhD, DMSc,[a] and Jens Lundgren, MD, DMSc[a]

[a]*Centre of Excellence for Health, Immunity and Infections (CHIP), Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark;* [b]*Department of Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*

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Abstract

Purpose: The incidence, etiology, and association of infections with radiation therapy (RT)−induced lymphopenia in patients with solid tumors is not well elucidated.

Methods and Materials: We identified possible, probable, and definite infections caused by bacteria, fungi, and viruses, combining data on medication, microbiology, and diagnoses. Definite infections had either a diagnosis or a positive microbiological isolation. We analyzed the incidence and adjusted incidence-rate ratio of infections in the year after the start of RT among patients who received RT plus chemotherapy and RT monotherapy, by type of infection and according to the degree of RT-induced lymphopenia.

Results: A total of 4450 of 6334 (70.3%) patients experienced 11264 infections overall; 1424 (22.5%) patients developed 2104 definite infections in the first year after RT. Infections were more frequent among patients who received RT plus chemotherapy (2590 of 3469; incidence: 16.5 [95% confidence interval {CI}, 16.1-17.0], per 100 patient-years) compared with patients who received RT monotherapy (1860 of 2865; incidence: 12.7 [95% CI, 12.3-13.2]). The incidence of infection was highest in the first 3 months overall (28.2 vs 18.0 in patients who received RT plus chemotherapy compared with those who received RT monotherapy) and for definite infections (4.7 vs 3.8). The proportion of specific bacterial infections were similar among patients who received RT plus chemotherapy versus those who received RT monotherapy. Urinary tract infections were the most frequent (51.2% vs 56.2%), followed by pneumonias (24.1% vs 22.4%). Viral and fungal infections were more frequent among patients who received RT plus chemotherapy, but they were uncommon. In multivariable analyses, patients who received RT plus chemotherapy with a lymphopenia grade of 1-2 or ≥3 versus no lymphopenia at end of RT had an increased risk of bacterial infections 0 to 3 months after RT (incidence rate ratio, 1.45 [95% CI, 1.06-1.97] and 1.71 [95% CI, 1.26-2.34], respectively). Limiting to definite bacterial infections, the incidence rate ratio for lymphopenia grade ≥3 versus no lymphopenia was 2.66 (95% CI, 1.40-5.03).

Conclusions: The incidence of bacterial infections 0 to 3 months after RT plus chemotherapy for solid tumors was high, especially among patients with RT-induced lymphopenia grade 1-2 and ≥3.

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Data sharing statement: Research data are stored in the Centre of Excellence for Personalized Medicine for Infectious Complications in Immune Deficiency (PERSIMUNE) data lake and will be shared upon request to the corresponding author.

*Corresponding author: Cynthia Terrones-Campos, MD; E-mail: cynthia.terrones.campos@regionh.dk

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Introduction

Infections are potentially serious complications of treatment in patients with cancer, which contribute with significant morbidity and mortality.[1] It is well documented that bacterial infections are common among patients with cancer and neutropenia induced by chemotherapy, but there are very few studies on the incidence, cause, and risk factors of infections in patients treated with radiation therapy for solid tumors.

A previous study found that radiation-induced lymphopenia was associated with an increased risk of a composite of infections in the first 3 months after radiation therapy.[2] In the present study, we evaluated incidence of various types of infections, including their presumed cause from the start of radiation therapy until 1 year after radiation therapy, and assessed the association between radiation-induced lymphopenia and risk of infections.

Methods and Materials

We identified patients who received their first course of radiation therapy with curative intent for their first cancer diagnosis at Rigshospitalet, University of Copenhagen between 2010 and 2016. We excluded patients with hematological malignancies, in situ tumors, benign tumors, patients with a human immunodeficiency virus diagnosis, and organ-transplant recipients. We also excluded patients without follow-up after radiation therapy (Fig. E1).

Data sources

Data were extracted from the Centre of Excellence for Personalized Medicine for Infectious Complications in Immune Deficiency (PERSIMUNE) data lake, which combines single-center, regional, and national databases.[3] Data on medications including chemotherapy and anti-infectives were extracted from the Electronic Patient Medication module, complemented with the Danish National Database of Reimbursed Prescriptions because the Electronic Patient Medication module had a gap from May 2011 to December 2011 due to system change. Data on microbiological laboratory tests were obtained from the laboratory production system in the capital region (Mikrobiologisk Afdelings Data System in Danish) and the nationwide registry of microbiology data from all hospital-based microbiological laboratories in Denmark (Den danske mikrobiologidatabase in Danish). The Danish National Patient Registry (Landspatientregisteret in Danish) and the health database (Sundhedsdatabanken in Danish) provided clinical data from patients treated in the Danish health care system (Appendix E1).

Definition of infections and other variables

Data on medication, microbiology, and diagnoses were combined to identify events of infection. Infectious events were categorized as possible, probable, or definite and further as bacterial, fungal, or viral infections as detailed in Appendix E2 and Fig. E2. We cataloged an infection as definite if a diagnosis of infection was registered and/or a microbiological isolation of a most likely pathogen was identified. Infections of mixed cause contributed in >1 category (eg, bacterial and viral). We grouped patients according to the type of treatment received as radiation therapy monotherapy and radiation therapy plus chemotherapy combinations (induction or concomitant chemotherapy).

Other variables included in analyses were sex, age at radiation therapy start, cancer diagnosis (Appendix E3), chemotherapy (Appendix E4), and the Charlson Comorbidity Index (CCI; age and cancer components were excluded from the index to avoid collinearity). We identified pretreatment and end-of-radiation-therapy (EoRT) lymphocyte and neutrophil counts, as well as the neutrophil count 2 weeks before infection. Pretreatment peripheral blood count was the closest measurement to radiation start collected within 1 year before radiation. EoRT peripheral blood count was the closest measurement to radiation end collected between 2 weeks before and 6 months after radiation therapy ended. We grouped blood counts according to the Common Terminology Criteria of Adverse Events, version 5.0 (Appendix E5). We defined cancer treatment failure as receipt of a new course of chemotherapy or radiation therapy or a biopsy with a malignant morphology (excluding basal cell carcinomas) after a nontreatment period of 3 months for colorectal cancer and 2 months for the remaining cancers.

Outcomes

The primary outcome was the risk for infections within 12 months after the start of radiation therapy. Secondary outcomes included time of infection and type of pathogen.

Statistical analyses

Time of observation was calculated for each patient from the start of radiation therapy to infection. Patients were followed until they failed to cancer treatment, date of death, 1 year after radiation therapy start, or at study closure (31.DEC.2016), whichever came first. We analyzed the risk of infection (of any cause) by cancer diagnosis at any time during follow-up using Kaplan-Meier methods, including all categories of infection and separately for definite infections.

We split observation time after initiating radiation therapy into 4 quarters from 0 to 3, 3 to 6, 6 to 9, and 9 to 12 months and calculated the total number of person-years at risk spent in each quarter. We calculated cause-specific incidence of infections for each time interval. Because multiple events of the same cause in the same quarter may be correlated, we censored follow-up at the first event of a specific cause per quarter, but we continued follow-up in subsequent quarters and for infections of other causes. For example: someone with a bacterial infection in the first quarter contributed time at risk from the beginning of the first quarter until the event but continued to be at risk for fungal or viral infections in the first and all causes in subsequent quarters. Incidences for each quarter were then calculated by dividing the number of patients developing an event by the number of person-years at risk.

We repeated etiology-specific incidence of infections according to the degree of EoRT lymphopenia at the aforementioned time intervals. We measured time from the start of radiation therapy but included only infections that occurred after the EoRT lymphocyte count date.

We analyzed the risk of cause-specific infection by the degree of EoRT lymphopenia in multivariable analyses using Poisson regression (see formula in Appendix E6). We included length of follow-up as offset (ie, ln(varname) with coefficient constrained to 1) and added the time intervals as dummy covariables. Results are presented as incidence-rate ratios with 95% confidence intervals. We checked for overdispersion using negative binomial regression. We identified the best fitting model for bacterial infections of any category (possible, probable, or definite) according to Akaike and Bayesian Information Criteria. We confirmed that this was also the best fit for definite bacterial infections alone and for the models split into radiation therapy monotherapy and radiation therapy plus chemotherapy. This model was then also used for fungal and viral infections of any category (possible, probable, or definite). We applied a Bonferroni correction with a P value of <.01 to prevent false positive findings owing to several regressions performed. We also estimated the effect of the EoRT neutrophil count, and the neutrophil count collected within 2 weeks before the infection, on the risk of cause-specific infections. To isolate the effect of radiation therapy on infections and the association of lymphopenia and infections, analyses were performed separately for patients treated with radiation therapy monotherapy and patients treated with radiation therapy plus chemotherapy. To test for sensitivity toward a bias arising from the availability of EoRT lymphocyte counts, we performed a first sensitivity analysis in which each patient with EoRT lymphocyte count is weighted to balance age, sex, CCI, and cancer diagnosis.

In a second sensitivity analysis, we excluded patients with breast cancer for the radiation therapy monotherapy group because they receive radiation therapy with different characteristics, with very low volume of the body irradiated with 2 Gy or more, owing to the predominance of tangential field techniques used in the department, which can have an effect on the EoRT lymphocyte count. Analyses were conducted using Stata software (version 17.0; StataCorp, College Station, TX).

Results

Study population

We included a total of 6334 patients. Of these, 2865 (45.2%) patients received radiation therapy monotherapy, of whom 1238 (43.2%) were patients with breast cancer. Patient characteristics are described in Table 1 according to type of treatment and according to cancer diagnosis in Tables E1 and E2. Patients differed by treatment type and by all characteristics displayed in Table 1, except for sex and mean equivalent dose in 2-Gy fractions. Notably, patients who received radiation therapy plus chemotherapy had a significantly lower EoRT lymphocyte count compared with patients treated with radiation therapy monotherapy (0.6×10^3 cells/μL [interquartile range, 0.4-1.0] vs 0.9×10^3 [interquartile range, 0.6-1.4], $P < .001$). For 1197 (18.9%) patients, follow-up was shorter than 12 months because of death (n = 333 vs 251), relapse (n = 176 vs 90) or censoring date (n = 244 vs 103), with a higher proportion among patients in the radiation therapy plus chemotherapy group compared with patients in the radiation therapy monotherapy group.

Incidence of infections of any category (possible, probable, or definite)

A total of 4450 patients (70.3%) experienced 11264 infections of any category in the first year after start of radiation therapy: 4383 versus 3243 bacterial infections in the radiation therapy plus chemotherapy group compared with the radiation therapy monotherapy group, 1087 versus 708 fungal, 199 versus 116 viral, and 987 versus 541 mixed infections (775 vs 406 bacterial and fungal, 129 vs 94 bacterial and viral, 6 vs 3 fungal and viral, and 77 vs 38 from all 3 causes). Infections were more frequent among patients who received radiation therapy plus chemotherapy (2590 of 3469 [74.7%]) compared with patients who received radiation therapy monotherapy (1860 of 2865 [64.9%]) (Fisher exact test $P < .001$).

More than half of the patients experienced at least 1 bacterial infection (68.8% vs 59.8% in the radiation therapy plus chemotherapy group compared with the radiation therapy monotherapy group), one-fourth experienced a fungal infection (31.3% vs 22.5%), and very few experienced a viral infection (8.5% vs 6.2%). Most of these infections were categorized as possible infections (Tables 2 and 3). The distribution of data contributing to the infection definition is shown in Figs. E3 and E4.

Table 1 Characteristics of patients by type of treatment

Characteristic	Radiation therapy plus chemotherapy	Radiation therapy monotherapy	*P* value
Number of patients	3469	2865	
Cancer diagnosis			<.001
Breast	1003 (28.9)	1238 (43.2)	
Head and neck	568 (16.4)	626 (21.9)	
Brain tumor	526 (15.2)	238 (8.3)	
Esophageal	425 (12.3)	13 (0.5)	
NSCLC	271 (7.8)	138(4.8)	
Cervix or endometrial	251 (7.2)	70 (2.4)	
Colorectal	205 (5.9)	39 (1.4)	
Prostate	0 (0)	186 (6.5)	
SCLC	73 (2.1)	45 (1.6)	
Other	147 (4.2)	272 (9.5)	
Female sex	2044 (58.9)	1754 (61.2)	.063
Age, y			<.001
0-49	832 (24.0)	426 (14.9)	
50-59	1062 (30.6)	502 (17.5)	
60-69	1091 (31.5)	1023 (35.7)	
≥70	484 (14.0)	914 (31.9)	
CCI, points			<.001
0	2570 (74.1)	1861 (65.0)	
1	591 (17.0)	587 (20.5)	
≥2	308 (8.9)	417 (14.6)	
Number of fractions	30 (25-33)	25 (15-33)	<.001
Total dose, Gy	56 (50-66)	50 (40-66)	<.001
Mean EQD2, Gy	58 (50-66)	53 (42-66)	<.060
Body V2			<.001
Number of patients (%)	2945 (84.9)	2465 (86.0)	
Median (IQR), L	7.2 (4.1-11.9)	4.7 (2.8-7.3)	
Course duration, d	38 (33-43)	37 (22-42)	<.001
Chemotherapy, yes (%)			
Induction	1586 (45.7)	0 (0)	<.001
Concomitant	2385 (68.8)	0 (0)	<.001
Adjuvant	190 (5.5)	19 (0.7)	<.001
Pretreatment lymphocyte count (among those with an available EoRT lymphocyte count)			
Number of patients (%)	1670 (48.1)	705 (24.6)	
Median (IQR), $\times 10^3$ cells/μL	1.7 (1.2-2.3)	1.7 (1.3-2.3)	<.001
EoRT lymphocyte count			
Number of patients (%)	2036 (58.7)	982 (34.3)	
Median (IQR), $\times 10^3$ cells/μL	0.6 (0.4-1.0)	0.9 (0.6-1.4)	<.001

Abbreviations: Body V2 = volume of the body exposed to 2 Gy or more; CCI = Charlson Comorbidity Index; EoRT = end of radiation therapy; EQD2 = equivalent dose in 2-Gy fractions; IQR = interquartile range; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer.
P values are from χ^2 tests (categorical variables) and Wilcoxon rank sum tests (continuous and count variables).

Table 2 Infections 1 year after the start of radiation therapy plus chemotherapy, according to cancer diagnosis, cause, and infection definition

Infections	Breast	Head and neck	Brain tumors	Esophageal	NSCLC	Cervix or endometrial	Colorectal	SCLC	Total
Number of patients	1003	568	526	425	271	251	205	73	3469
Any infection, number of patients (%)	545 (54.3)	528 (93.0)	419 (79.7)	347 (81.6)	200 (73.8)	203 (80.9)	178 (86.8)	59 (80.8)	2590 (74.7)
Any definite infection, number of patients (%)	84 (8.4)	168 (29.6)	120 (22.8)	134 (31.5)	77 (28.4)	79 (31.5)	81 (39.5)	23 (31.5)	821 (23.7)
Bacterial infections, number of infections (number of patients)									
Possible, probable, or definite	921 (503)	1052 (443)	858 (404)	717 (314)	408 (191)	523 (198)	461 (175)	127 (54)	5364 (2388)
Probable or definite	200 (145)	481 (309)	243 (158)	363 (212)	174(114)	250 (141)	226 (118)	59 (33)	2138 (1312)
Definite	92 (73)	219 (158)	177 (115)	182 (129)	101 (75)	123 (76)	133 (80)	76 (53)	1133 (779)
Fungal infections, number of infections (number of patients)									
Possible, probable, or definite	136 (101)	962 (454)	116 (71)	332 (204)	130 (81)	66 (52)	68 (47)	55 (31)	1945 (1086)
Probable or definite	26 (23)	276 (222)	32 (24)	140(113)	52 (42)	38 (33)	41 (37)	24 (19)	665 (542)
Definite	3 (3)	11 (11)	4 (4)	8 (8)	4 (4)	2 (2)	3 (3)	5 (5)	44 (44)
Viral infections, number of infections (number of patients)									
Possible, probable, or definite	131 (71)	58 (49)	66 (49)	55 (48)	39 (26)	28(22)	16 (13)	8 (7)	411 (295)
Probable or definite	16 (14)	11 (11)	9 (9)	15 (13)	8 (7)	3 (3)	2 (2)	3 (3)	68 (63)
Definite	12 (10)	9 (9)	6 (6)	14 (12)	7 (6)	3 (3)	1 (1)	2 (2)	55 (50)

Abbreviations: NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer.

Table 3 Infections 1 year after the start of radiation therapy monotherapy, according to cancer diagnosis, cause, and infection definition

Infections	Breast	Head and neck	Brain tumors	Esophageal	NSCLC	Cervix orendometrial	Colorectal	Prostate	SCLC	Total
Number of patients	1238	626	238	13	138	70	39	186	45	2865
Any infection, number of patients (%)	654 (52.8)	550 (87.9)	137 (57.6)	9 (69.2)	110 (79.7)	56 (80.0)	29 (74.4)	108 (58.1)	19 (42.2)	1860 (64.9)
Any definite infection, number of patients (%)	138 (11.1)	193 (30.8)	44 (18.5)	7 (53.8)	55 (39.9)	32 (45.7)	8 (20.5)	36 (19.4)	13 (28.9)	603 (21.0)
Bacterial infections, number of infections (number of patients)										
Possible, probable, or definite	1196 (629)	1115 (464)	247 (126)	15 (8)	284 (108)	152 (56)	67 (27)	201 (100)	50 (24)	3781 (1714)
Probable or definite	312 (224)	473 (286)	91 (61)	9 (7)	110 (67)	83 (39)	16 (14)	82 (45)	25 (15)	1428 (870)
Definite	179 (136)	257 (182)	63 (42)	7 (7)	74 (55)	63 (32)	9 (8)	58 (35)	17 (12)	883 (585)
Fungal infections, number of infections (number of patients)										
Possible, probable, or definite	93 (67)	798 (423)	47 (32)	2 (1)	46 (32)	27 (12)	14 (7)	9 (9)	45 (19)	1155 (646)
Probable or definite	20 (19)	189 (158)	9 (9)	0 (0)	19 (16)	10 (9)	2 (2)	2 (2)	9 (8)	299 (251)
Definite	1 (1)	16 (15)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	22 (21)
Viral infections, number of infections (number of patients)										
Possible, probable, or definite	96 (53)	71 (57)	23 (17)	0 (0)	8 (8)	5 (5)	2 (2)	15 (11)	3 (3)	251 (178)
Probable or definite	7 (7)	17 (15)	5 (5)	0 (0)	1 (1)	0 (0)	0 (0)	5 (3)	0 (0)	43 (36)
Definite	4 (4)	11 (9)	4 (4)	0 (0)	1 (1)	0 (0)	0 (0)	5 (3)	0 (0)	31 (24)

Abbreviations: NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer.

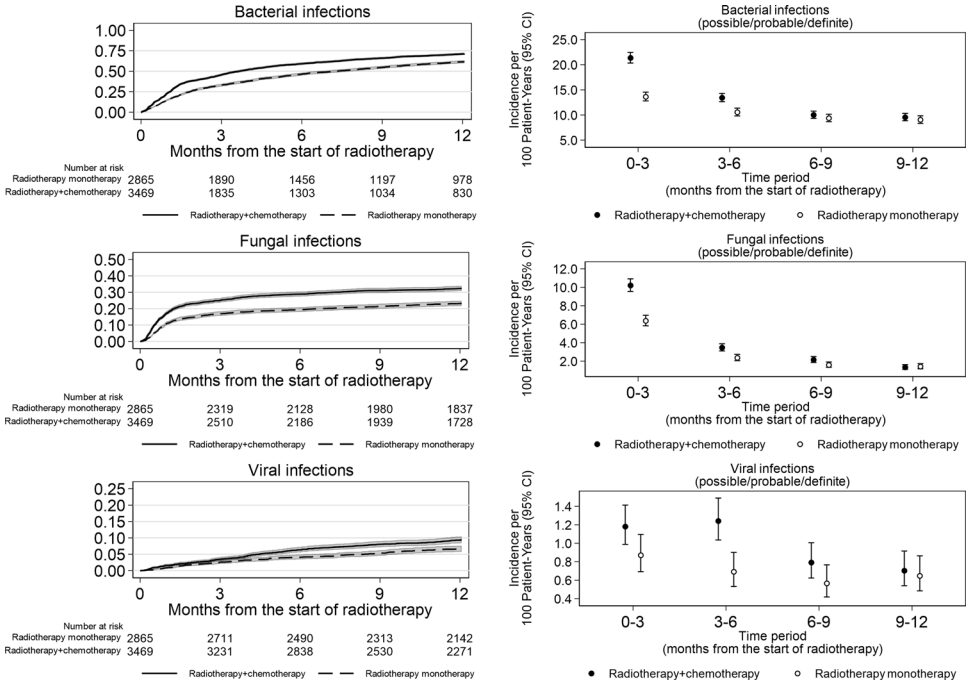

Fig. 1 Kaplan-Meier (KM) survival probability curves and incidence of infections according to cause, type of treatment and time after radiotherapy start. Including any infection (possible, probable, or definite).

In the whole cohort, the incidence of infection per 100 patient-years was 14.71 (95% confidence interval [CI], 14.39-15.04). Of patients at risk, 47.5% (3008 of 6334) experienced an infection during the first 3 months (incidence: 23.18 [95% CI, 22.37-24.02] per 100 patient-years), decreasing over time to 10.34 (95% CI, 9.80-10.91) between 9 and 12 months.

Patients treated with radiation therapy plus chemotherapy had a higher incidence of infection compared with patients treated with radiation therapy monotherapy (incidence: 16.54 [95% CI, 16.07-17.02] vs 12.73 [95% CI, 12.30-13.17]). Different incidences of infection were observed in the first semester after the start of radiation therapy: 28.24 (95% CI, 26.98-29.55) versus 17.98 (95% CI, 16.97-19.05) in the 0 to 3 months, and 15.92 (95% CI, 15.04-16.85) versus 12.28 (95% CI, 11.47-13.15) in the 3 to 6 months. Afterward, incidences of infection were similar between therapy groups (data not shown). Risk of infection varied by cancer diagnosis (Fig. E5). Patients with head and neck cancer had the highest risk of infection (96.9% [95% CI, 96.0-97.7] and 94.3% [95% CI, 93.2-95.3] by 12 months in the radiation therapy plus chemotherapy group and radiation therapy monotherapy group, respectively), whereas patients with breast cancer had the lowest risk (64.2% [95% CI, 61.8-66.7] and 62.8% [95% CI, 60.1-65.0]).

Patients treated with radiation therapy plus chemotherapy compared with patients treated with radiation therapy monotherapy had a higher incidence of bacterial (13.66 [95% CI, 13.24-14.09] vs 10.72 [95% CI, 10.33-11.12]), fungal (4.36 [95% CI, 4.14-4.59] vs 2.97 [95% CI, 2.78-3.18]), and viral infections (1.00 [95% CI, 0.90-1.11] vs 0.70 [95% CI, 0.61-0.80]). We observed higher incidences of bacterial and fungal infections among patients treated with radiation therapy plus chemotherapy compared with patients treated with radiation therapy monotherapy in the 0 to 3 months (21.36 [95% CI, 20.33-22.45] vs 13.64 [95% CI, 12.80-14.54] for bacterial infections, and 10.21 [95% CI, 9.55-10.91] vs 6.38 [95% CI, 5.83-6.97] for fungal infections, respectively) and in the 3 to 6 months after the start of radiation therapy (13.45 [95% CI, 12.65-14.29] vs 10.57 [95% CI, 9.83-11.34] for bacterial infections, and 3.47 [95% CI, 3.11-3.88] vs 2.34 [95% CI, 2.05-2.74] for fungal infections, respectively). For viral infections, the contrasting incidence was observed in the 3 to 6 months after the start of radiation therapy (1.24 [95% CI, 1.03-1.49] vs 0.69 [95% CI, 0.53-0.90]; Fig. 1).

Definite infections

Overall, 1424 patients (22.5%) developed 2104 definite infections in the first year after the start of radiation therapy: 1094 versus 862 bacterial infections in the radiation therapy plus chemotherapy group compared with the radiation therapy monotherapy group, 22 versus 12 fungal, 34 versus 20 viral and 39 versus 21 mixed infections (17 vs 11 bacterial and fungal, 18 vs 10 bacterial and viral, and 4 vs 0 from all 3 causes). Definite infections were also more frequent among patients who received radiation

therapy plus chemotherapy (821 of 3469 [23.7%]) compared with patients who received radiation therapy monotherapy (603 of 2865 [21.0%]) (Fisher exact test $P = .013$).

In the whole cohort, the infection incidence per 100 patient-years was 2.76 (95% CI, 2.64-2.89). A total of 11.8% of patients (746 of 6334) experienced an infection during the first 3 months (incidence: 4.26 [95% CI, 3.97-4.58] per 100 patient-years), decreasing over time to an incidence of 1.81 (95% CI, 1.61-2.04) between 9 and 12 months. Risk of infection varied by cancer diagnosis (Fig. E5). Among patients who received radiation therapy plus chemotherapy, patients with colorectal cancer had the highest risk of infection by 12 months (45.6% [95% CI, 39.5-52.1]), whereas among patients who received radiation therapy monotherapy, the highest risk of infection was observed in patients with cervix or endometrial cancer (56.4% [95% CI, 46.3-66.9]). Patients with breast cancer had the lowest risk (12.7% [95% CI, 11.0-14.7] and 9.6% [95% CI, 8.0-11.6]) in both treatment groups.

The incidence of infection per 100 patient-years among patients who received radiation therapy plus chemotherapy was 2.96 (95% CI, 2.79-3.15), slightly higher than among patients who received radiation therapy monotherapy (2.53 [95% CI, 2.36-2.72]). Divergent incidences were only observed in the first 3 months after the start of radiation therapy. A total of 12.8% (445 of 3469) of patients treated with radiation therapy plus chemotherapy experienced an infection during the first 3 months (incidence: 4.68 [95% CI, 4.27-5.14] per 100 patient-years), compared with 10.5% (301 of 2865) of patients treated with radiation therapy monotherapy (3.76 [95% CI, 3.36-4.21]).

The incidence of definite infections followed the same pattern as when including all categories of infection. Among patients who received radiation therapy plus chemotherapy and patients who received radiation therapy monotherapy, bacterial infections predominated, causing 95.3% (1133 of 1189) and 96.5% (883 of 915) of all definite infections, respectively. A total of 21.1% (1133 of 5364) and 23.1% (883 of 3816) of all bacterial infections were categorized as definite.

Incidences of definite bacterial, fungal, and viral infections were similar across treatment groups. The incidence of bacterial infections was the highest for both patients who received radiation therapy plus chemotherapy (2.80 [95% CI, 2.63-2.98]) and patients who received radiation therapy monotherapy (2.45 [95% CI, 2.28-2.64]). It was higher in the first 3 months after start of radiation therapy (4.4 [95% CI, 4.0-4.9] and 3.6 [95% CI, 3.2-4.1], respectively) and decreased over time (Fig. E6). We observed no temporal trend for definite fungal or viral infections.

Infection site and pathogens of definite infections

As shown in Fig. 2, the proportion of specific bacterial infections were similar among patients who

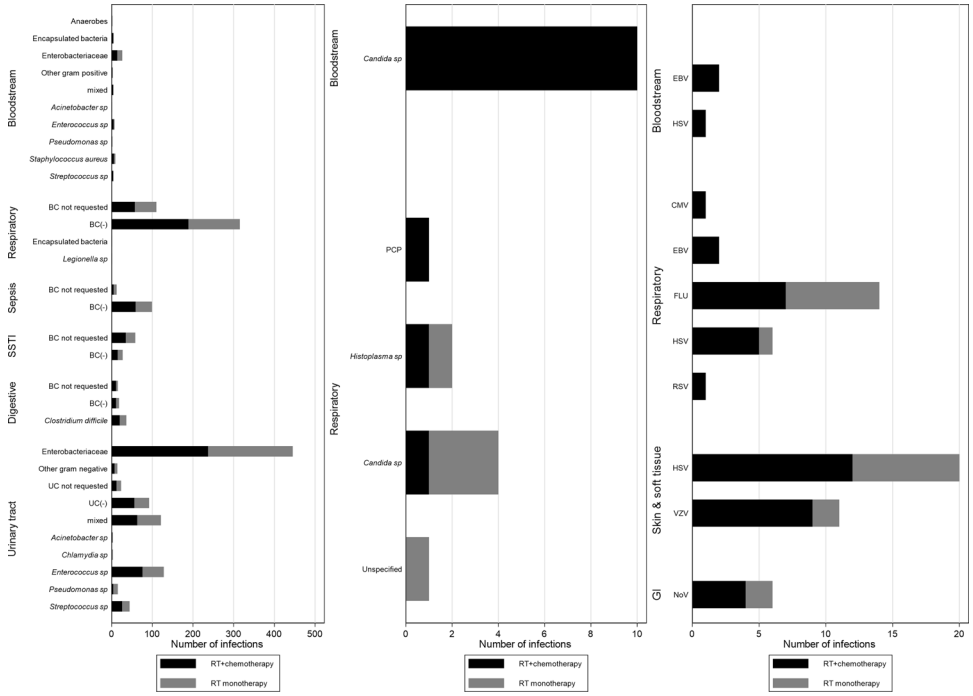

Fig. 2 Definite infections, cause, and type of pathogen according to type of treatment: 3 meningoencephalitis, 5 tuberculosis, 78 unspecific bacterial infections, and 22 viral infections are not plotted on the graph. *Abbreviations*: BC = blood culture; SSTI = skin and soft tissue infection; UC = urine culture.

received radiation therapy plus chemotherapy versus patients who received radiation therapy monotherapy. Urinary tract infections (UTIs) were the most frequent. The proportion of patients with at least 1 UTI was highest among patients with colorectal cancer (34.3%) in the radiation therapy and chemotherapy group and among patients with cervix or endometrial cancer (47.9%) in the radiation therapy monotherapy group. *Enterobacteriaceae* were identified in 48.3% (280 of 580) and 50.8% (252 of 496) of UTIs, followed by *Enterococcus spp* in 14.7% (85 of 580) and 13.5% (67 of 496) in patients treated with radiation therapy plus chemotherapy and radiation therapy monotherapy, respectively. Pneumonias were the second most frequent infection. Proportion of pneumonia was highest in patients with non-small cell lung cancer (20.7%) among patients treated with radiation therapy plus chemotherapy and in patients with esophageal cancer (39.4%) among patients treated with radiation therapy monotherapy. Bloodstream infections and *Clostridium difficile* infection were uncommon. The proportion of patients with at least 1 episode of bacteremia was highest among patients with colorectal cancer (5.7%) in the radiation therapy plus chemotherapy group and among patients with small cell lung cancer (7.1%) in the radiation therapy monotherapy group. *Enterobacteriaceae* were identified in 31.8% (14 of 44) and 50.0% (13 of 26) bacteremias in patients treated with radiation therapy plus chemotherapy and radiation therapy monotherapy, respectively, followed by *Enterococcus spp* in 18.2% (8 of 44) and 15.4% (4 of 26) and *Staphylococcus aureus* in 15.9% (7 of 44) and 15.4% (4 of 26). The risk of specific bacterial infections was also highest in the 3 months after the start of radiation therapy (Table 4).

Fungal and viral infections seemed more frequent among patients who received radiation therapy plus chemotherapy, but there were only a few definite infections from these causes. Viral infections followed bacterial infections in frequency. They were more frequent in the first 6 months after the start of radiation therapy. Fungal infections were the least common of all definite infections; 33 of 66 (50.0%) versus 13 of 66 (19.7%) were *Candida* infections in patients treated with radiation therapy plus chemotherapy compared with radiation therapy monotherapy, 12 of 33 versus 3 of 13 were invasive *Candida* infections, and 10 of 12 versus 0 of 3 were candidemia. The cause of definite infections and temporal trends of specific definite infections can be found in Fig. 2 and Fig. E7.

Associations between radiation-induced lymphopenia and risk of infection

A total of 3018 of 6334 (47.6%) patients with an available EoRT lymphocyte count contributed to these analyses. Almost 60% of patients treated with radiation therapy plus chemotherapy (2036 of 3469 [58.7%]) had an available EoRT lymphocyte count, compared with only one-third of patients treated with radiation therapy monotherapy (982 of 2865 [34.3%]). The percentages of patients with an available pretreatment lymphocyte count from the start of radiation therapy date, and an EoRT lymphocyte count from the EoRT date are provided in Fig. E8.

When including all categories of infection, 2036 patients in the radiation therapy plus chemotherapy group developed 2533 bacterial, 774 fungal, and 215 viral infections, whereas 982 patients in the radiation therapy monotherapy group developed 1171 bacterial, 274 fungal, and 89 viral infections. The incidence of infection was higher among patients with an available EoRT lymphocyte count versus patients without an available EoRT lymphocyte count (Fig. E9). Among patients who received radiation therapy and chemotherapy, patients with EoRT lymphopenia grade 1 to 2 (incidence: 18.91 [95% CI, 16.22-22.05]) and patients with EoRT lymphopenia grade ≥3 (22.79 [95% CI, 19.96-26.02]) had a higher incidence of bacterial infections in the 0 to 3 months after the start of radiation therapy, compared with patients without EoRT lymphopenia (12.40 [95% CI, 9.52-16.16]).

The number of definite infections was low. We identified 603 bacterial, 23 fungal, and 32 viral infections among patients treated with radiation therapy plus chemotherapy, and 321 bacterial, 8 fungal, and 13 viral infections among patients treated with radiation therapy monotherapy. We only estimated the incidence of definite bacterial infections, which led to similar findings. Among patients who received radiation therapy plus chemotherapy, patients with EoRT lymphopenia grade 1 to 2 (18.91 [95% CI, 16.22-22.05]) and patients with EoRT lymphopenia grade ≥3 (22.79 [95% CI, 19.96-26.02]) had a higher incidence of bacterial infections in the 0 to 3 months after the start of radiation therapy compared with patients without EoRT lymphopenia (12.40 [95% CI, 9.52-16.16]).

We also performed multivariable analyses separately for patients according to the type of treatment received, accounting for an interaction of time after the start of radiation therapy and the EoRT lymphocyte count, and adjusting for age, sex, and CCI (Tables 5 and 6). Among patients treated with radiation therapy plus chemotherapy, when analyzing all categories of infection, patients with EoRT lymphopenia grade 1 to 2 or ≥3 had a higher incidence of bacterial infections compared with patients without EoRT lymphopenia in the first 3 months after the start of radiation therapy (incidence rate ratio [IRR], 1.45 [95% CI, 1.06-1.97]; P = .019; and IRR, 1.71 [95% CI, 1.26-2.34]; P = .001, respectively). In the period of 3 to 6 months, these patient groups also had a higher incidence of fungal infections (IRR, 2.05 [95% CI, 1.22-3.45]; P = .002; and IRR, 2.21 [95% CI, 1.33-3.67]; P = .007, respectively) and viral infections (IRR, 2.55 [95% CI, 1.22-5.33]; P = .012; and IRR, 2.27 [95% CI, 1.02-5.03]; P = .044, respectively). When restricting to definite

Table 4 Incidence of infections 1 year after the start of radiation therapy according to infection definition and type of treatment

	Radiation therapy plus chemotherapy			Radiation therapy monotherapy		
	Patients, n	Incidence per 100 person-years (95% confidence interval)	Number of infections within first 3 mo/total of infections in a year (%)	Patients, n	Incidence per 100 person-years (95% confidence interval)	Number of infections within first 3 mo/total of infections in a year (%)
Infection of any cause						
Possible, probable, or definite	2590	16.54 (16.07-17.02)	1857/4615 (40.2)	1860	12.73 (12.30-13.17)	1151/3265 (35.3)
Definite	821	2.96 (2.79-3.15)	445/1026 (43.4)	603	2.53 (2.36-2.72)	301/762 (39.5)
Bacterial infections						
Possible, probable, or definite	2388	13.66 (13.24-14.09)	1570/4007 (39.2)	1714	10.72 (10.33-11.12)	939/2847 (33.0)
Probable or definite	1312	5.33 (5.08-5.58)	824/1775 (46.4)	870	4.01 (3.79-4.24)	459/1178 (39.0)
Definite	779	2.80 (2.63-2.98)	424/973 (43.6)	585	2.45 (2.28-2.64)	290/739 (39.2)
Urinary tract infection	407	1.41 (1.29-1.54)	405/498 (81.3)	333	1.34 (1.25-1.52)	168/421 (39.9)
Pneumonia	230	0.72 (0.63-0.81)	106/257 (41.2)	177	0.61 (0.53-0.71)	73/190 (38.4)
Bacteremia	41	0.12 (0.09-0.16)	17/41 (41.5)	24	0.08 (0.06-0.12)	7/26 (26.9)
CDI	18	0.07 (0.04-0.10)	7/24 (29.2)	14	0.06 (0.04-0.10)	9/19 (47.4)
Fungal infections						
Possible, probable, or definite	1086	4.36 (4.14-4.59)	862/1455 (59.2)	646	2.97 (2.78-3.18)	481/880 (54.7)
Probable or definite	542	1.76 (1.63-1.91)	409/620 (66.0)	251	0.91 (0.81-1.02)	152/280 (54.3)
Definite	44	0.12 (0.09-0.16)	24/44 (54.5)	21	0.07 (0.05-0.11)	9/22 (40.9)
Candidemia	10	0.03 (0.01-0.05)	5/10 (50.0)	0		
Viral infections						
Possible, probable, or definite	295	1.00 (0.90-1.11)	119/357 (33.3)	178	0.70 (0.61-0.80)	73/216 (33.8)
Probable or definite	63	0.18 (0.14-0.23)	20/66 (30.3)	36	0.13 (0.09-0.17)	14/39 (35.9)
Definite	50	0.15 (0.11-0.19)	17/53 (32.1)	24	0.09 (0.06-0.13)	12/27 (44.4)
Influenza	7	0.02 (0.01-0.04)	4/7 (57.1)	7	0.02 (0.01-0.05)	2/13 (15.4)
HSV	12	0.03 (0.02-0.06)	4/12 (33.3)	8	0.03 (0.01-0.05)	4/8 (50.0)

Abbreviations: CDI = Clostridium difficile infection; HSV = Herpes simplex virus.

Table 5 Poisson regression allowing for up to 1 event per quarter among patients treated with radiation therapy plus chemotherapy, with interactions between EoRT lymphocyte count and quarter

Characteristic	Bacterial infections Possible, probable, or definite IRR (95% CI)	Probable or definite IRR (95% CI)	Definite IRR (95% CI)	Fungal infections Possible, probable, or definite IRR (95% CI)	Viral infections Possible, probable, or definite IRR (95% CI)
0-3 mo					
EoRT lymphopenia G 1-2	1.45 (1.06-1.97)*	1.39 (0.86-2.24)	1.74 (0.92-3.31)	1.42 (0.85-2.40)	1.37 (0.49-3.86)
EoRT lymphopenia G ≥3	1.71 (1.26-2.34)†	2.14 (1.34-3.43)†	2.66 (1.40-5.03)†	1.63 (0.97-2.74)	1.82 (0.65-5.10)
3-6 mo					
EoRT lymphopenia G 1-2	1.08 (0.87-1.35)	1.35 (0.96-1.89)	1.13 (0.74-1.72)	2.21 (1.33-3.67)†	2.55 (1.22-5.33)*
EoRT lymphopenia G ≥3	1.12 (0.89-1.41)	1.28 (0.89-1.82)	1.23 (0.79-1.91)	2.05 (1.22-3.45)†	2.27 (1.02-5.03)†
6-9 mo					
EoRT lymphopenia G 1-2	1.03 (0.81-1.30)	1.07 (0.73-1.56)	1.10 (0.69-1.74)	1.05 (0.65-1.72)	1.67 (0.75-3.73)
EoRT lymphopenia G ≥3	1.00 (0.77-1.30)	0.99 (0.66-1.48)	1.21 (0.74-1.98)	0.99 (0.61-1.63)	1.70 (0.70-4.15)
9-12 mo					
EoRT lymphopenia G 1-2	1.09 (0.84-1.41)	1.14 (0.74-1.75)	1.35 (0.77-2.39)	0.98 (0.51-1.86)	1.31 (0.54-3.17)
EoRT lymphopenia G ≥3	1.09 (0.82-1.44)	1.24 (0.80-1.94)	1.55 (0.86-2.78)	0.72 (0.37-1.41)	1.35 (0.51-3.57)
Female sex	1.11 (0.98-1.25)	1.03 (0.86-1.23)	1.14 (0.92-1.43)	1.28 (1.05-1.57)*	1.75 (1.20-2.55)†
Age, y					
0-50	Ref.	Ref.	Ref.	Ref.	Ref.
0-60	0.91 (0.77-1.09)	0.87 (0.67-1.13)	1.14 (0.81-1.61)	0.80 (0.60-1.08)	1.27 (0.74-2.18)
0-70	1.04 (0.88-1.24)	1.16 (0.91-1.49)	1.63 (1.18-2.24)†	0.72 (0.54-0.96)	1.30 (0.77-2.18)
>70	1.11 (0.91-1.35)	1.19 (0.90-1.57)	1.77 (1.25-2.52)†	0.67 (0.47-0.96)*	1.18 (0.67-2.09)
CCI					
0	Ref.	Ref.	Ref.	Ref.	Ref.
1	1.13 (0.98-1.29)	1.17 (0.96-1.43)	1.35 (1.06-1.72)*	1.07 (0.83-1.38)	1.42 (0.96-2.11)
≥2	1.31 (1.12-1.54)†	1.49 (1.17-1.88)†	1.55 (1.16-2.08)†	1.41 (1.04-1.92)*	1.29 (0.79-2.10)
Cancer diagnosis					
Breast	Ref.	Ref.	Ref.	Ref.	Ref.
Head and neck	1.15 (0.88-1.49)	1.46 (0.95-2.23)	1.10 (0.65-1.87)	7.36 (4.09-13.23)†	0.45 (0.20-0.99)*
Brain tumors	1.18 (0.94-1.50)	1.41 (0.95-2.09)	1.74 (1.09-2.79)*	1.83 (0.99-3.38)	0.78 (0.40-1.52)

(*continued on next page*)

Table 5 (*Continued*)

Characteristic	Bacterial infections Possible, probable, or definite IRR (95% CI)	Probable or definite IRR (95% CI)	Definite IRR (95% CI)	Fungal infections Possible, probable, or definite IRR (95% CI)	Viral infections Possible, probable, or definite IRR (95% CI)
Esophageal	1.31 (1.01-1.70)*	2.01 (1.31-3.09)†	1.65 (0.99-2.77)	4.93 (2.68-0.07)†	0.78 (0.37-1.66)
NSCLC	1.21 (0.92-1.59)	1.71 (1.11-2.63)*	1.64 (0.97-2.79)	2.87 (1.52-5.43)†	0.71 (0.35-1.46)
Cervix or endometrial	1.31 (0.94-1.82)	2.20 (1.33-3.62)†	2.01 (1.10-3.69)*	0.80 (0.35-1.80)	0.49 (0.19-1.24)
Colorectal	1.76 (1.33-2.33)†	2.77 (1.78-4.32)†	2.72 (1.61-4.59)†	2.22 (1.10-4.48)*	0.37 (0.12-1.13)
SCLC	1.33 (0.93-1.89)	1.76 (1.02-3.04)*	1.72 (0.92-3.23)	5.25 (2.53-10.90)†	0.56 (0.20-1.56)

Abbreviations: CCI = Charlson Comorbidity Index; CI = confidence interval; EoRT = end of radiation therapy; G = grade; IRR = incidence rate ratio; NSCLC = non-small cell lung cancer; Ref. = reference; SCLC = small cell lung cancer.

* Significant IRR, $P < .05$.

† Significant IRR, $P < .01$.

Further adjusted for age, sex, CCI, and cancer diagnosis. The reference categories for the estimates of EoRT lymphopenia grades indicate no lymphopenia.

infections, patients with EoRT lymphopenia grade ≥3 still had a higher incidence of bacterial infections compared with patients without EoRT lymphopenia in the 0 to 3 months after the start of radiation therapy (IRR, 2.66 [95% CI, 1.40-5.03]; $P = .003$). No associations were found in the other time intervals.

Among patients treated with radiation therapy monotherapy, we found patients with EoRT lymphopenia grade 1 to 2 compared with patients without EoRT lymphopenia had a higher incidence of definite bacterial infections in the 3 to 6 months after the start of radiation therapy (IRR, 1.67 [95% CI, 1.03-2.68]; $P = .036$).

The proportion of patients with neutropenia grade ≥3 after radiation therapy or within 2 weeks before a bacterial infection was low. Among 3018 patients with available EoRT neutrophil count, only 130 patients (4.3%) had EoRT neutropenia grade ≥3, the majority of whom (126 of 130 [96.9%]) had received radiation therapy plus chemotherapy. In addition, 883 of 3018 patients (29.3%) had a neutrophil count measured close to infection; of these, 33 patients (3.7%) had neutropenia grade ≥3, with 24 [87.9%] in the radiation therapy plus chemotherapy group.

Among 1910 patients who received radiation therapy plus chemotherapy and had EoRT neutropenia grade 1 to 2 or no neutropenia, patients with EoRT lymphopenia grade 1 to 2 and patients with EoRT lymphopenia grade ≥3 still had a higher incidence of bacterial infections than patients without EoRT lymphopenia (IRR, 1.50 [95% CI, 1.10-2.06]; $P = .011$; and IRR, 1.82 [95% CI, 1.32-2.50]; $P < .001$, respectively). Findings were consistent when looking at 585 patients who received radiation therapy and chemotherapy and had a neutrophil count close to infection for EoRT lymphopenia grade 1 to 2, and EoRT lymphopenia grade ≥3 compared with no lymphopenia (IRR, 1.54 [95% CI, 1.01-2.35]; $P = .047$; and IRR, 1.89 [95% CI, 1.22-2.93]; $P = .005$, respectively). We did not find a significant association among patients who received radiation therapy monotherapy. We could not perform analyses of patients with neutropenia grade ≥3 at EoRT or close to infection owing to the low number of patients.

In the first sensitivity analysis using inverse probability weight for EoRT lymphocyte count availability in the Poisson regression models, we found similar results (data not shown). The logistic regression to predict the availability of EoRT lymphocyte counts, including cancer diagnoses, age, sex, and CCI had a good area under the receiver operating characteristic curve of 0.79. Associations also remained consistent in the second sensitivity analysis excluding patients with breast cancer for the radiation therapy monotherapy group (Table E3).

Discussion

In this study of 6334 patients treated with radiation therapy for solid malignant tumors, we found a high

Table 6 Poisson regression allowing for up to 1 event per quarter among patients treated with radiation therapy monotherapy, with interactions between EoRT lymphocyte count and quarter

Characteristic	Bacterial infections Possible, probable, or definite IRR (95% CI)	Probable or definite IRR (95% CI)	Definite IRR (95% CI)	Fungal infections Possible, probable, or definite IRR (95% CI)	Viral infections Possible, probable, or definite IRR (95% CI)
0-3 mo					
EoRT lymphopenia G 1-2	1.15 (0.77-1.71)	1.23 (0.67-2.24)	0.92 (0.46-1.83)	0.98 (0.53-1.81)	3.47 (0.66-18.25)
EoRT lymphopenia G ≥3	1.18 (0.75-1.86)	1.62 (0.86-3.06)	1.31 (0.64-2.67)	0.81 (0.41-1.61)	2.49 (0.39-15.74)
3-6 mo					
EoRT lymphopenia G 1-2	1.24 (0.95-1.63)	1.60 (1.07-2.40)	1.67 (1.03-2.68)*	1.29 (0.77-2.16)	0.82 (0.33-2.04)
EoRT lymphopenia G ≥3	0.90 (0.61-1.33)	1.51 (0.89-2.53)	1.59 (0.87-2.93)	0.59 (0.27-1.29)	1.62 (0.59-4.46)
6-9 mo					
EoRT lymphopenia G 1-2	1.07 (0.80-1.42)	1.49 (0.98-2.27)	1.64 (0.98-2.74)	1.59 (0.81-3.14)	0.87 (0.28-2.71)
EoRT lymphopenia G ≥3	1.47 (1.00-2.16)	1.45 (0.83-2.53)	1.30 (0.63-2.67)	1.73 (0.77-3.89)	1.92 (0.54-6.86)
9-12 mo					
EoRT lymphopenia G 1-2	0.97 (0.71-1.31)	1.35 (0.84-2.16)	1.03 (0.55-1.92)	1.15 (0.56-2.37)	0.98 (0.33-2.86)
EoRT lymphopenia G ≥3	0.79 (0.51-1.23)	1.07 (0.55-2.09)	0.71 (0.27-1.90)	0.89 (0.34-2.36)	0.44 (0.06-3.52)
Female sex	1.11 (0.90-1.37)	0.98 (0.75-1.29)	0.94 (0.68-1.29)	1.11 (0.79-1.55)	0.84 (0.44-1.59)
Age, y					
0-50	Ref.	Ref.	Ref.	Ref.	Ref.
0-60	1.02 (0.71-1.45	0.94 (0.57-1.57)	1.24 (0.65-2.36)	0.71 (0.37-1.36)	0.64 (0.27-1.48)
0-70	1.28 (0.93-1.77)	1.37 (0.87-2.16)	1.73 (0.97-3.10)	1.06 (0.57-2.00)	0.74 (0.33-1.70)
>70	1.29 (0.94-1.77)	1.42 (0.90-2.22)	1.78 (1.00-3.18)	0.78 (0.42-1.45)	0.44 (0.19-1.02)
CCI					
0	Ref.	Ref.	Ref.	Ref.	Ref.
1	1.21 (0.98-1.50)	1.05 (0.78-1.41)	1.00 (0.70-1.43)	1.10 (0.73-1.64)	1.15 (0.56-2.36)
≥2	1.61 (1.30-1.99)	1.54 (1.13-2.08)†	1.49 (1.03-2.15)*	1.11 (0.75-1.67)	2.07 (1.04-4.15)*
Cancer diagnosis					
Breast	Ref.	Ref.	Ref.	Ref.	Ref.
Head and neck	1.55 (1.17-2.06)†	1.88 (1.24-2.84)†	1.56 (0.95-2.55)	12.05 (5.87-24.73)†	0.92 (0.37-2.26)
Brain tumors	1.14 (0.81-1.62)	1.47 (0.89-2.41)	1.60 (0.89-2.87)	3.61 (1.42-9.20)†	0.53 (0.18-1.54)

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Table 6 (*Continued*)

Characteristic	Bacterial infections Possible, probable, or definite IRR (95% CI)	Probable or definite IRR (95% CI)	Definite IRR (95% CI)	Fungal infections Possible, probable, or definite IRR (95% CI)	Viral infections Possible, probable, or definite IRR (95% CI)
Esophageal	1.23 (0.63-2.40)	1.89 (0.65-5.47)	2.25 (0.82-6.18)	NE	NE
NSCLC	1.39 (1.02-1.90)*	1.87 (1.16-3.02)*	1.91 (1.09-3.34)*	5.21 (2.33-11.62)†	0.46 (0.14-1.51)
Cervix or endometrial	1.34 (0.80-2.22)	2.79 (1.47-5.28)†	2.59 (1.15-5.85)*	4.52 (1.31-15.61)*	0.49 (0.06-4.23)
Colorectal	1.50 (0.95-2.38)	0.97 (0.46-2.04)	0.68 (0.20-2.27)	0.93 (0.11-7.75)	NE
Prostate	0.99 (0.63-1.55)	1.04 (0.50-2.15)	0.98 (0.43-2.24)	1.10 (0.29-4.18)	0.75 (0.19-2.91)
SCLC	0.82 (0.43-1.58)	1.18 (0.50-2.76)	1.24 (0.45-3.37)	6.43 (2.53-16.33)†	0.42 (0.05-3.54)

Abbreviations: CCI = Charlson Comorbidity Index; CI = confidence interval; EoRT = end of radiation therapy; G = grade; IRR = incidence rate ratio; NE = not estimable; NSCLC = non-small cell lung cancer; Ref. = reference; SCLC = small cell lung cancer.

* Significant IRR, $P < .05$.

† Significant IRR, $P < .01$.

Further adjusted for age, sex, CCI, and cancer diagnosis. The reference categories for the estimates of EoRT lymphopenia grades indicate no lymphopenia.

incidence of infections in the first 3 months after the start of radiation therapy, which decreased over time. EoRT lymphocyte counts were significantly lower among patients who received radiation therapy plus chemotherapy, and probably as a consequence, infections were more frequent in this group compared with patients treated with radiation therapy monotherapy. The incidence of infections was associated with the degree of EoRT lymphopenia.

Only a minor proportion of infections was categorized as definite. Bacterial infections predominated, followed by viral and fungal infections. Urinary tract infections caused by *Enterobacteriaceae* were the most common bacterial infections, and herpes simplex virus were the most frequent cause of viral infections. Candidemia was rare and only identified among patients treated with radiation therapy plus chemotherapy. As expected, the anatomic locations of the infections were highly influenced by the anatomic area being irradiated (eg, UTI in patients with cervix, endometrial, or colorectal cancer, and pneumonia in patients with lung cancer and esophageal cancer).

Patients with head and neck cancer had the largest difference in the proportion of patients with an infection of any category and definite infections. This group of patients almost invariably develop oral and pharyngeal radiation-induced mucositis, which may worsen by the addition of concomitant chemotherapy or targeted therapy, and as there is often an element of fungal infection contributing to the severe symptoms, many patients are treated empirically with fluconazole.[4,5] Viral infection contributing to the mucositis may also be suspected and antiviral therapy administered.[6] In many cases the treatment is given empirically without any attempt to obtain a microbiological diagnosis, which may explain the high number of infections when considering any category of infection.

Definite infections were based on diagnoses and microbiological detection of pathogens. A stringent definition may underestimate the real magnitude of infections. It depends on registration, available guidelines and testing capability. Furthermore, patients with cancers other than head and neck cancer as described previously may also have received empirical antibiotic therapy, which has shown to lower dramatically the chance of a confirmed microbiological diagnosis.[7] Plausible explanations for the low proportion of definite infections include the fact that the diagnosis of infection was often based on clinical signs or symptoms, rather than microbiological testing, as well as the poor sensitivity of cultures, which could be as low as 50% for blood cultures[8]; this highlights the need for more sensitive diagnostic methods.

Most studies evaluating the burden of infections among patients with cancer describe infections in the context of bacteremia and include patients with hematological malignancies, who have a higher incidence of infection than patients with solid tumors.[9-12] In our study,

we broadly investigated infection risk in an heterogenous cohort of patients with solid tumors.

The most frequent isolated bacteria were Gram-negative bacteria from the family of *Enterobacteriaceae* for both urinary tract and bloodstream infections, followed by Gram-positive bacteria *Enterococci spp* for urinary tract infections and *Staphylococcus aureus* for bacteremia. Our findings are in line with studies investigating patients with cancer who developed bacteremia that lately show a shift from Gram-positive to Gram-negative bacteria as the predominant organisms.[13] Of note, we excluded coagulase-negative *Staphylococcus* when analyzing bloodstream infections because we could not ascertain the circumstances of blood sample collection nor account for the presence of indwelling catheters. Susceptibility and resistance patterns of pathogens were not our current focus, but it may be a future research topic for further studies given the world-wide emergence of antibiotic resistance. Invasive fungal infections were infrequent in our cohort, as well as viral infections.

EoRT lymphopenia was associated with a higher risk of infections after radiation therapy plus chemotherapy. We cannot attribute lymphopenia solely to radiation in our cohort. However, lymphopenia after radiation therapy is a recognized long-lasting phenomenon that occurs owing to the high susceptibility of lymphocytes to radiation, exacerbated by chemotherapy[14-16] as found in this study. Patients who received radiation therapy plus chemotherapy had a lower EoRT lymphocyte count compared with patients who received radiation therapy monotherapy, although EoRT lymphocyte counts were remarkably lower than pretreatment counts among both treatment groups.

Low numbers of lymphocyte count correlate with a higher degree of inflammation, dysregulating the host response which may lead to an inflammatory state, which may lead to negative outcomes.[17] Among patients with human immunodeficiency virus diagnosis, the decrease and impairment of lymphocytes results in infections.[5] In the general population, a large Danish study found lymphopenia (<1100 cells/μL) was associated with increased risk of hospital admission with an infection and increased risk of death,[18] and in the United States, lymphopenia (≤1500 cells/μL) was associated with decreased survival, independent of clinical variables.[19] Among patients with cancer, a study of African children showed profound lymphopenia (<100 cells/μL) was associated with a higher risk of dying with microbiological confirmed sepsis.[9] In this sense, it is feasible that lymphopenia due to an impaired immune response can lead to an increase in the risk of infection and complications.

Lymphopenia is not the only culprit of infections but in the absence of other relevant factors that are known to carry an increased risk of infection, such as neutropenia (<500 cells/μL), it becomes of relevance. In our cohort, very few patients presented with neutropenia grade ≥3 (<1000 cells/μL) at the EoRT or within 2 weeks of infection. Neutrophils are not lowered to significant thresholds by radiation, but they could decrease secondary to myelosuppressive chemotherapy. Rapid proliferation of neutrophils may contribute to their sustained counts, in contrast to lymphocytes. We cannot rule out the possibility that even when counts of neutrophils remain normal, the functionality of neutrophils might be affected due to the underlying cancer or its treatment.

Other factors may play a role in the risk of infections. Most episodes of bloodstream infections in patients with solid tumors occur in nonneutropenic patients and seem health care related.[12] In a study of bloodstream infections among patients with solid tumors, a large proportion of the patients had been hospitalized within the last 3 months of infection.[20] In our study we did not investigate previous hospital admissions but we found infections were most common in the 3 months after the start of radiation therapy, which is the period of time when patients are most in contact with health services receiving radiation therapy combined or not with chemotherapy.

The strengths of this study are the large number of patients with different types of solid tumors, the broad assessment of the burden of infections after radiation therapy separately by type of treatment and cause and presenting infections in different categories.

Limitations to acknowledge are that many patients in the radiation therapy monotherapy group did not have EoRT lymphocyte counts available. We accounted for this by applying inverse probability weights in the multivariable models. Furthermore, among patients treated with radiation therapy monotherapy, breast cancer was the most common diagnosis. These patients receive radiation therapy with different characteristics, with very low volume of the body irradiated with 2 Gy or more, due to the predominance of tangential field techniques used in the department, which may spare the effect of radiation on the lymphocytes. In a sensitivity analysis excluding patients with breast cancer, we still found no association between EoRT lymphopenia and infections.

We may have overestimated the incidence of some infections, particularly of fungal etiology. First, because we could not identify patients who received antifungal drugs empirically during radiation therapy or for minor infections such as oral thrush. Most of the fungal infections were identified based on prescription of antifungal drugs and categorized as possible. Second, by considering fungal infections as probable if a culture was performed. Blood cultures commonly do not detect disseminated *Candida* infection, although the BacT/Alert system detects candidemia earlier and more frequently than conventional systems. In Denmark, all centers where samples were processed either worked with BACTEC or BacT/Alert before our inclusion date.[21] We accounted for this when analyzing definite infections.

Adjuvant chemotherapy could have further decreased lymphocyte counts thus increasing the risk of infection,

which would not have been attributed to our measured EoRT lymphocyte count. This could have led to an underestimation of the incidence of infections. However, very few patients in our cohort received adjuvant chemotherapy. Finally, we cannot rule out false positive findings because of the large numbers of regressions performed in this study but a Bonferroni correction still supports our results.

Conclusion

The incidence of infections in our cohort was high but decreased when limiting to definite infections, occurring mostly in the first 3 months after the start of radiation therapy. Infections were more common among patients who received radiation therapy plus chemotherapy, in whom they were associated with EoRT lymphopenia. Lymphocyte counts are rarely done systematically during or after radiation therapy, but our results indicate that these provide useful information, alerting the treating physician of patients at high risk of infection. Future prospective studies should evaluate subtypes of lymphocytes compromised during radiation therapy, as well as the integrity of the immune response after radiation in specific cancer diagnosis.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2022.100950.

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