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Radiation Therapy and the Risk of Herpes Zoster in Patients With Cancer

Takuya Shimizuguchi, MD[1]; Noritaka Sekiya, MD [2,3]; Konan Hara, MD, PhD[4,5]; Ayumi Taguchi, MD, PhD[6]; Yujiro Nakajima, MS[1,7]; Yu Miyake, MD[1]; Yukiko Shibata, MD[1]; Kentaro Taguchi, MD[1]; Hiroaki Ogawa, MD[1]; Kei Ito, MD, PhD[1]; and Katsuyuki Karasawa, MD, PhD[1]

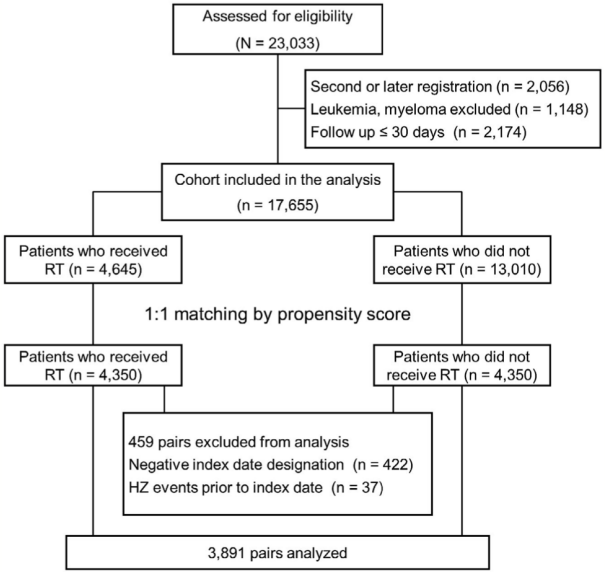
BACKGROUND: The role and impact of radiation therapy (RT) on the development of herpes zoster (HZ) has not been well studied. The objective of this study was to investigate the association between RT and HZ. **METHODS:** A propensity score-matched, retrospective cohort study was conducted using institutional cancer registry data and medical records from 2011 to 2015. The risk of developing HZ in the RT and non-RT groups was compared using a Cox proportional hazards model. Associations also were explored between the RT field and the anatomic location of HZ in patients who developed HZ after RT. The expected number of HZ events within the radiation field was calculated according to the RT received by each patient; then, this number was compared with the observed number of in-field events. **RESULTS:** Of 17,655 patients, propensity score matching yielded 4350 pairs; of these, 3891 pairs were eligible for comparison. The cumulative incidence of HZ in the RT group (vs the non-RT group) during the first 5 years after the index date was 2.1% (vs 0.7%) at 1 year, 3.0% (vs 1.0%) at 2 years, 3.4% (vs 1.3%) at 3 years, 4.1% vs 1.7% at 4 years, and 4.4% vs 1.8% at 5 years. The RT group showed a significantly higher risk of HZ than the non-RT group (hazard ratio, 2.59, 95% CI, 1.84-3.66). In the 120 patients who developed HZ after RT, HZ events were observed significantly more frequently within the RT field than expected (74 vs 43.8 events; $P < .001$). **CONCLUSIONS:** Patients with cancer who received RT showed a significantly higher risk of HZ, which was commonly observed within the radiation field. ***Cancer* 2020;0:1-8**. © *2020 American Cancer Society*.

KEYWORDS: herpes zoster; neoplasms, radiation, radiotherapy, varicella zoster virus.

Introduction

- Several studies have investigated the development of herpes zoster (HZ) after radiation therapy (RT) and have described the frequency and timing of events and the clinical course.
- However, most of those studies were limited to cohorts of patients with a specific malignant disease and lacked robust statistical analyses.
- We assessed the relation between receipt of RT and the development of HZ in patients with cancer using a 2-pronged approach:
  1. we compared the prevalence of HZ in propensity score-matched RT and non-RT recipients;
  2. we assessed whether the anatomic location of an HZ event was related to the radiation field.

Problem of Survival Analysis With Matching—Lead-time Bias



Comparison of RT Field and Anatomic Location of HZ

- Theoretically, we can state that the irradiated body area is related to the body area affected by an HZ event if a difference exists between the marginal distribution of the body area affected by HZ events and its distribution conditional on the irradiated body area.
- To implement this idea empirically, we devised a simple statistical test for all eligible patients who received RT before the development of HZ.
- We computed the marginal probability of an HZ event occurring on the irradiated body area from the empirical marginal distribution of the 5 anatomic body areas (trigeminal, cervical, thoracic, lumbar, and caudal) affected by HZ events.

Empirical Marginal Distribution of Body Area Affected by HZ

- We categorized the body surface into 64 mutually exclusive parts based on spinal cord segments: bilateral trigeminal 1–3, cervical 2–8, thoracic 1–12, lumbar 1–5, and sacral 1–5.
- Each HZ event was categorized into the most appropriate segment according to the affected dermatomal location.
- The empirical marginal distribution of the body area affected by HZ events was calculated as an empirical probability mass function of an HZ event occurrence on any of the 64 segments.
- Because of the scarcity of data, we imposed the probability of an HZ event occurrence per segment to be the same within five large anatomical groups: trigeminal, cervical, thoracic, lumbar, and sacral.

Empirical Marginal Distribution of Body Area Affected by HZ

Probability of an HZ event occurrence on segment s, $\Pr(s)$, was calculated as follows:

$$\Pr(s) = \frac{n_g}{N} \times \frac{1}{d_g}$$

- g is an anatomical group that includes segment s
- n_g is the observed number of HZ events categorized into group g
- N is the total number of HZ events
- d_g is the number of dermatome segments included in group g

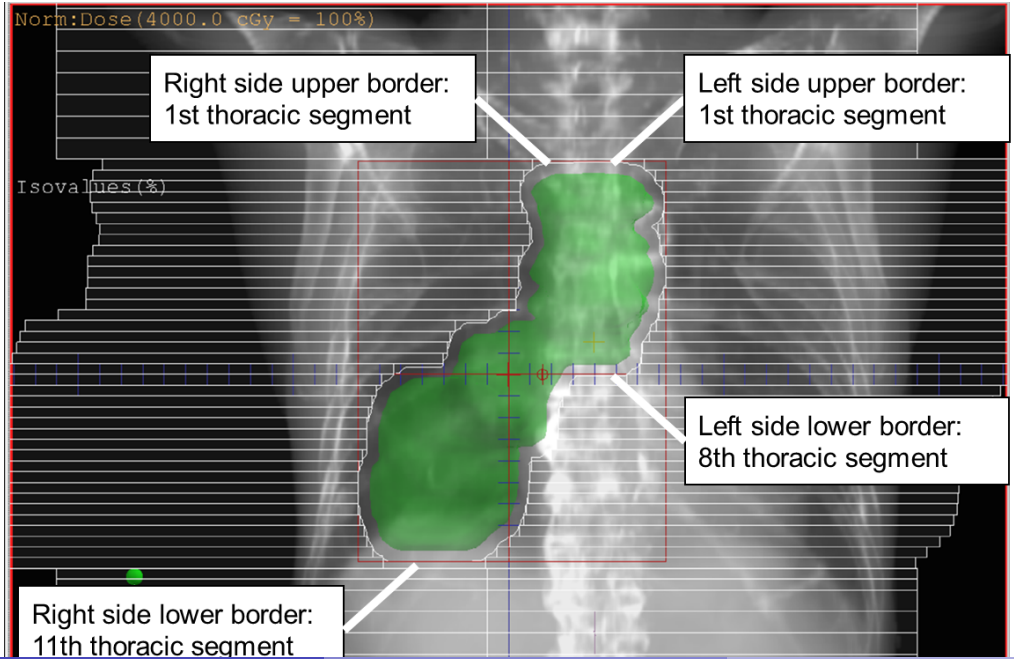
Supporting Table 1. Anatomical location of herpes zoster events in all eligible patients and calculated empirical marginal probability per dermatome segment for each anatomical group

Anatomical group	d_g	n_g	Pr(s)
Trigeminal	6	51	0.029
Cervical	14	33	0.008
Thoracic	24	137	0.020
Lumbar	10	44	0.015
Sacral	10	24	0.008
Unspecified	-	5	-
Total	64	294	-

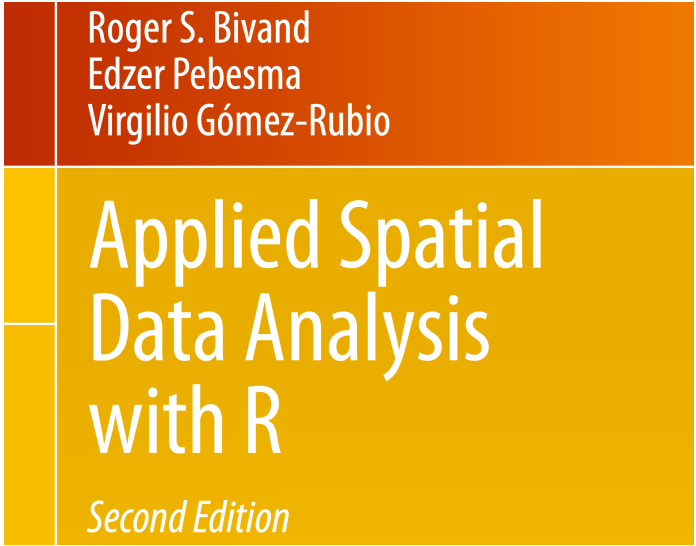
Abbreviations: d_g = number of dermatome segments included in group g; n_g = number of herpes zoster events categorized in group g; Pr(s) = empirical marginal probability of an herpes zoster event per dermatome segment.

Comparison of RT Field and Anatomic Location of HZ Events

- A post-RT HZ event was categorized as an in-field event if it occurred in the radiation field or as an out-field event otherwise.
- If the null hypothesis (the irradiated body area is unrelated to the body area affected by HZ events) were true, then the totaled marginal probability of in-field events can be considered as the expected number of in-field events in the cohort.
- We can test the null hypothesis by comparing this value with the observed number of in-field events.


Norm:Dose(4000.0 cGy = 100%)
Isovalues(%)
Right side upper border:
1st thoracic segment
Left side upper border:
1st thoracic segment
Left side lower border:
8th thoracic segment
Right side lower border:
11th thoracic segment

Statistical Testing



Disease Mapping

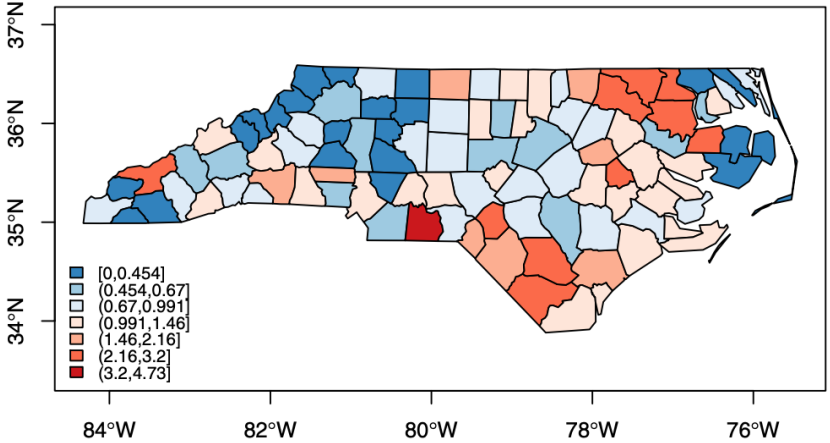


Fig. 10.1 Standardised Mortality Ratio of the North Carolina SIDS data in the period 1974–1978

Testing the Homogeneity of the Relative Risks[1]

- Disease mapping provides a first insight to the spatial distribution of the disease but it may be required to locate the presence of zones where the risk tends to be unusually higher than expected.
- We can test whether there are actual differences among the different relative risks.
- Given that for each area we have computed its expected and observed number of cases (O_i, observed; E_i, expected), a chi-square test can be carried out to test for (global) significant differences between these two quantities:

$$\chi^2 = \sum_{i=1}^{n} \frac{(O_i - E_i)^2}{E_i} \overset{a}{\sim} \chi^2_{n-1}$$

  - internal standardization is used to obtain E_i: $\sum_{i=1}^{n} O_i = \sum_{i=1}^{n} E_i$

1. Bivand, Pebesma, and Gomez-Rubio Section 10.6.1

Results: RT and Anatomic Distribution of HZ Events

- The total number of HZ events in the 17,655 eligible patients was 294, which was used to calculate the empirical marginal probability of HZ events.
- Of 294 events, 123 were observed after RT, and 120 of those (3 events were excluded because of unspecified HZ distribution) were used to test the null hypothesis.
- The expected number of in-field versus out-field HZ events under the null hypothesis for the 120 patients was 43.8 versus 76.2 events, respectively.
- The observed number of in-field versus out-field HZ events was 74 versus 46 events, respectively, which was significantly higher than the expected number of in-field HZ events ($P < .001$).