TITLE

Season of radiotherapy and outcomes of head & neck cancer patients in the MACH-NC & MARCH meta-analyses

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* Meta-Analysis of Chemotherapy in Squamous Cell Head and Neck Cancer
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Highlights

- The season of radiotherapy delivery (fall/winter versus spring/summer) was queried.
- Season of treatment does not influence PFS nor LRF in head and neck cancer.
- No impact was seen even in Northern countries where differences are expected to be greater.

Keywords: radiation therapy, head and neck cancer, season of treatment

Abstract

Background

A single institution retrospective study suggested that head and neck squamous cell cancer (HNSCC) patients receiving radiotherapy (RT) during “dark” season (fall/winter) may have better outcomes than those treated during ”light” season (spring/summer), possible secondary to seasonal variations in cell cycle progression. We investigated the impact of season of RT in two large, multi-institutional, prospective datasets of randomized trials.

Methods

Individual patient data from the MACH-NC and MARCH meta-analyses were analyzed. Dark season was defined as mid-radiotherapy date during fall or winter and light the reverse, using equinoxes to separate the two periods.

Primary endpoint was progression-free survival (PFS) and secondary endpoint was locoregional failure (LRF). The effect of season was estimated with a Cox model stratified by trial and adjusted on sex, tumor site, stage, and treatment. Planned sensitivity analyses were performed on patients treated around solstices, received “complete radiotherapy”, treated with concomitant radio-chemotherapy and on trials performed in Northern countries.

Results

11320 patients from 33 trials of MARCH and 6138 patients from 28 trials of MACH-NC were included. RT during dark season had no benefit on PFS in the MARCH (hazard ratio[HR]: 1.01 [95%CI 0.97;1.05],p=0.72) or MACH-NC dataset (HR:1.00 [95%CI 0.94;1.06],p=0.99. No difference in LRF was observed in the MARCH (HR:1.00 [95%CI 0.94;1.06,p=0.95) or MACH-NC dataset (HR:0.99 [95%CI 0.91; 1.07],p=0.78). Sensitivity analyses showed similar results.

Conclusion

Season of RT had no impact on PFS or LRF in two large databases of HNSCC.

Introduction

Head and neck squamous cell cancer (HNSCC) accounts for approximately 800,000 cases and 400,000 deaths annually worldwide [1]. The standard of care for locally-advanced disease for oral cavity, oropharynx, hypopharynx, and larynx subsites is a multimodality treatment with permutations of radiation therapy (RT), chemotherapy (CT), and surgery, in function of tumor localization. Treatment sequelae in these highly functional zones may significantly affect quality of life; and despite optimal treatment, mortality remains high. The search for factors influencing efficacy and toxicity outcomes continues.

In 2021, Elicin et al published a single institution retrospective study in Switzerland on 655 patients with HNSCC treated with radiotherapy (+/- chemotherapy) between 2002 and 2015 showing that the effect of seasonality of radiotherapy on loco-regional control (5-year LRC, 73% vs. 61%; p = 0.0108) and progression-free survival (5-year PFS, 51% vs. 43%; p = 0.0374) was superior when radiotherapy was administered during the darker half of the year than during the lighter half [2]. This period was likewise associated with increased acute toxicity (Toxicity (T), Adverse long-term effects (A), and Mortality risk (M) generated by a treatment program (E=End results) (TAME)) T score 1.98 vs 1.61, p = 0.0127) [3]. A possible explanation is a variation in cell cycle progression in function of seasons, possibly related to vitamin D levels, with epidemiologic studies showing improved survival for cancers diagnosed during the summer and autumn in Norway [4] and in the United Kingdom [5]. Another possibility seen in preclinical studies is that the disruption of the circadian rhythm leads to accelerated tumor growth [6,7]. However, the retrospective single center nature of the reported studies are at risk of false positivity.

The aim of this paper is to investigate the impact of the season of radiotherapy delivery in outcomes of HNSCC treated with radiotherapy in two large, multi-institutional prospective datasets of randomized trials. Individual patient data from two previously published meta-analyses, The Meta-Analysis of Chemotherapy in squamous cell Head and Neck Cancer (MACH-NC) [8,9] and The Meta-Analysis of Radiotherapy in squamous cell Carcinomas of Head and neck (MARCH) [10,11], were used.

Materials and Methods

Patients and trials

Inclusion criteria for each subset was previously described[8,9,11,12] and detailed in the Supplementary data. Briefly, patients with non-metastatic oral cavity, oropharynx, hypopharynx, or larynx HNSCC undergoing first-line curative treatment with available duration of RT were included. The data initially collated consisted of age, sex, tumor site, T and N classification, stage, histology, performance status, allocated treatment, date of randomization, and dose and duration of radiotherapy. The date and site of the first recurrence and second primary were recorded, as well as survival status and date of last follow-up. Patients with missing data on sex, tumor site, stage or season of treatment were excluded from the analyses. Details on the trials included are in Supplementary Tables S1 and S2. MACH-NC and MARCH steering committees approved the proposed research question, and a protocol for statistical analysis was written prior to analysis. The work has been carried out in accordance with the Declaration of Helsinki.

Definition of season

Dark season was defined, similar to the definition of by Elicin et al [2], as mid-radiotherapy date between September 22nd, year X and March 20th, year X+1 for studies performed in the Northern hemisphere. Light season was defined as a mid-radiotherapy date between March 20th, year X and September 22nd, year X. For the trials performed in the Southern hemisphere, RIO [13] and TROG [14], these Dark/Light definitions were inverted. As radiotherapy dates were often not available, mid-radiotherapy date was estimated for each patient using the date of randomization and the radiotherapy duration. When radiotherapy duration was not available, the theoretical duration planned in the trial protocol was used.

Outcomes

Progression-free survival was the primary endpoint. Progression-free survival was defined as the time between randomization and progression, death from any cause or last follow-up, whichever occurred first. Locoregional failure (LRF) was the secondary endpoint defined as locoregional failure alone or associated with metastatic failure as first event. If distant failure alone or death without failure occurred before LRF, patient was censored at the date of these events. Patients alive without failure were censored at the date of last follow-up.

Statistical analysis

The impact of dark/light season of radiotherapy on outcomes was estimated with a Cox proportional hazards model stratified by trial for univariate analysis and then adjusted on sex (male, female), tumor site (oral cavity, oropharynx, larynx, hypopharynx, other), stage (I-II, III-IV),

treatment (control arm, experimental arm) for multivariable analysis. Hazard ratios (HR) and their 95% confidence intervals (CI) were estimated. Factors for adjustment in Cox models were similar to those used by Elicin, et al, except for the AM/PM covariate which was not available in the MARCH and MACH-NC datasets, and the treatment arm was added. Chi-square heterogeneity test was used to test for statistical heterogeneity of season effect among trials. We also calculated the I^2 statistic expressing the proportion of variability in the season effect attributable to heterogeneity rather than to the sampling error, with an I^2 value below 30% considered indicative of low heterogeneity[15].

Several sensitivity analyses were performed. As radiotherapy dates were often not available, there was some uncertainty as to the attribution of the light or dark season in patients treated around the equinoxes. Thus, we performed a sensitivity analysis restricted to patients treated around the solstices (May, June and July versus November, December and January). Another sensitivity analysis was based on patients who received "complete radiotherapy" defined as at least 90% of the planned radiotherapy dose in MARCH or at least 60 Gy in MACH-NC, in less than 10 weeks. Patients with a missing dose or a missing duration were excluded from this analysis. Finally, in the MACH-NC dataset, an analysis based only on patients of the experimental arms (RT+ concomitant CT) and in the MARCH dataset, an analysis based only on trials performed in Northern countries (Northern Europe and Canada), where differences in daytime between dark and light seasons are more pronounced, were performed.

Five-year PFS and LRF rates were estimated using Kaplan-Meier method. All P values are two-sided. Analyses were done with the SAS 9.4 software.

Results

Patient, tumor and radiotherapy characteristics

There were 11320 patients from 33 trials of MARCH and 6138 patients from 28 trials of MACH-NC included in the analysis (Figure 1).

Patient characteristics are summarized in Table 1. Median age was 59 years old (interquartile range (IQR) 52; 66) and 56 (IQR 49; 63) for MARCH and MACH-NC datasets, respectively. For the two datasets, more than 80% of patients were male, and the predominant tumor site was oropharynx followed by larynx. Majority were AJCC Stage IV, and the median RT dose was 68 Gy (IQR 64; 70) for MARCH and 66 Gy (IQR 60; 70) for MACH-NC with a median duration of 43 (IQR 36; 48) and 46 (IQR 39; 52) days, respectively. In each dataset, the patient, tumor and

radiotherapy characteristics were similar between patients treated during the dark and the light season (Table S3).
The median follow-up was 7.8 years (IQR 5.3-11.7) in the MARCH dataset and 8.3 years (IQR 5.0-11.7) in the MACH-NC dataset.

Progression-free survival

There was no evidence of a benefit on PFS of the dark season for radiotherapy delivery in the MARCH dataset (HR: 1.01 [95%CI 0.97; 1.05], p=0.72) or in the MACH-NC dataset (HR: 1.00 [95%CI 0.94; 1.06], p=0.99) (Table 2). In the MARCH dataset, the 5-year PFS rates were 35.6% for patients treated during the light season and 35.5% for patients treated during the dark season. In the MACH-NC dataset, the 5-year PFS rates were 26.1% and 27.3% in the light and dark seasons respectively. In multivariable analysis in both datasets, patient sex, tumor site and tumor stage were strong prognostic factors for PFS.

When the analysis was restricted to patients treated around the solstices, the HR of PFS events were still around 1 in the MARCH dataset (1.03 [95%CI 0.97; 1.09]) and in the MACH-NC dataset (1.06 [95%CI 0.98; 1.15]) (Table 3).

Dose or duration of radiotherapy were not available for 607 patients of the MARCH dataset and for 1655 patients of the MACH-NC dataset, and 516 and 1162 patients, respectively, did not receive “complete” radiotherapy. Thus, the sensitivity analysis in patients treated with “complete” radiotherapy were based on 10 197 patients from MARCH and 3 321 patients from MACH-NC. They showed no effect of the dark season on PFS, HR 1.00 (95%CI 0.95; 1.04, p=0.93) in MARCH and HR 0.99 (95%CI 0.92; 1.08, p=0.90) in MACH-NC. The results were similar when the analysis was restricted to patients treated around the solstices (Table 3).

In the MARCH dataset, when the analysis was limited to the five trials performed in Northern countries treated with “complete” radiotherapy (2 615 patients from ARTSCAN [16] (Sweden), DAHANCA 6&7 [17] and DAHANCA 9 [18] (Denmark), PMH Toronto [19] (Canada), BCCA 9113 [20] (Canada)), no significant effect of season on PFS was observed, with a HR of 0.93 (95%CI 0.85; 1.02, p=0.11) for the dark season in Cox model stratified by trial and adjusted on sex, tumor site, stage and treatment. The HR was closer to 1 when the analysis was restricted to patients treated around the solstices (0.99 [95%CI 0.87; 1.12]) (Table 3).

In the MACH-NC dataset, when the analysis was limited to the patients of the experimental arm (concomitant chemo-radiotherapy) treated with “complete” radiotherapy (1 641 patients), no

significant effect of season on PFS was observed, with a HR of 0.97 (95%CI 0.86; 1.08, p=0.55) for the dark season in Cox model stratified by trial and adjusted on sex, tumor site and stage. The result was similar when the analysis was restricted to patients treated around the solstices (Table 3).

Loco-regional failure

Data on LRF was available for 11 257 patients of the MARCH dataset and 5 132 patients of the MACH-NC dataset. There was no evidence of a decrease in LRF when patients were treated during the dark season as compared to the light season in the MARCH dataset (HR: 1.00 [95%CI 0.94; 1.06, p=0.95) or in the MACH-NC dataset (HR: 0.99 [95%CI 0.91; 1.07], p=0.78) (Table 4). In the MARCH dataset, the 5-year LRF rates were 43.1% for patients treated during the light season and 43.1% for patients treated during the dark season. In the MACH-NC dataset, the 5-year LRF incidence rates were 55.1% and 54.0% in the light and dark seasons respectively.

When the analysis was restricted to patients treated around the solstices, the HR of LRF were still around 1 in the MARCH dataset (1.02 [95%CI 0.94; 1.11]) and in the MACH-NC dataset (1.03 [95%CI 0.92; 1.16]) (Table 5).

The sensitivity analyses in patients treated with “complete” radiotherapy were based on 10163 patients from MARCH and 2963 patients from MACH-NC (Table 5). They showed no effect of the dark season on LRF, HR 1.00 (95%CI 0.94; 1.06, p=0.95) in MARCH and HR 0.98 (95%CI 0.88; 1.09, p=0.67) in MACH-NC. The results were similar when the analysis was restricted to patients treated around the solstices.

In the MARCH dataset, when the analysis was limited to the five trials performed in Northern countries (2 611 patients) treated by “complete” RT, no significant effect of season on LRF was observed, with a HR of 0.92 (95%CI 0.81; 1.04, p=0.19) for the dark season in Cox model stratified by trial and adjusted on sex, tumor site, stage and treatment. The HR was closer to 1 when the analysis was restricted to patients treated around the solstices (1.01 [95%CI 0.85; 1.21]).

In the MACH-NC dataset, when the analysis was limited to the patients of the experimental arm (concomitant chemo-radiotherapy) treated by “complete” radiotherapy (1477 patients), no significant effect of season on LRF was observed, with a HR of 0.91 (95%CI 0.78; 1.07, p=0.27) for the dark season in Cox model stratified by trial and adjusted on sex, tumor site and stage. The result was similar when the analysis was restricted to patients treated around the solstices.

Discussion

In this large multicentric analysis of individual patient data, no effect of season was seen in the outcomes of patients treated with radiation therapy for head and neck cancer. This is in contrast with the findings of Elicin et al, who found that treatment during the “dark” season (between September 22nd to March 20th of the following year) was associated with better tumor control and better PFS. Our results are not surprising, as there are no strong pathophysiologic or radiobiological rationale for their findings. One of the principal hypotheses is that the season of diagnosis and/or treatment affects outcomes through variation in vitamin D levels, which varies with sunlight exposure. The plausibility of this phenomenon remains unclear. In an epidemiological study in the United Kingdom on breast, colorectal, lung, and prostate primaries, when season of diagnosis and cumulative sunlight hours were mutually adjusted, the effect of season persisted but the sunlight effect did not [5]. Furthermore, patients diagnosed in summer and autumn showed increased survival compared with those diagnosed in the winter, which is in contrast with the results of Elicin, et al.

The effect of vitamin D was studied in HNSCC, where pre-treatment serum 25-hydroxyvitamin D and total vitamin D intake were measured for stage I and II patients undergoing RT. In multivariate analysis, no association was observed with recurrence (p=0.99), incidence of second primaries (p=0.64), or overall mortality (p=0.53) [21]. In contrast, a recently published systematic review with meta-analysis of case-control and cohort studies evaluating vitamin D levels and head and neck cancer (HNC) had mortality as a secondary outcome, and reported increased HNC survival in two studies (pooled HR 1.13, 95%CI 1.05; 1.22) and decreased HNC mortality in three studies (pooled HR 0.75, 95%CI 0.60 to 0.94) with high concentrations of circulating 25-hydroxyvitamin D [22]. These results should probably be interpreted with caution, as they are based on observational studies.

The impact of seasons and exposure to sunlight would probably be more marked in patients living closer to polar regions than closer to the equator, as seasonal differences are more pronounced. We tested this hypothesis with planned analysis on the Northern trials (Denmark, Sweden, Canada) in the MARCH subset (2 615 patients), but again did not find significant difference on PFS (HR 0.93 [95%CI 0.85; 1.02], p=0.11) or LRC (HR 0.92 [95%CI 0.81; 1.04], p=0.19), reiterating the lack of impact of season on treatment effect in HNSCC.

Another hypothesis is that tumor control and toxicities vary with the time of radiation therapy, possibly in relation to the variations in the circadian clock of the cell cycle. For example, the G2-

M phase, considered the most radiosensitive of the cell cycle, was shown to occur in the late afternoon and evening in human oral mucosa, as measured by increased secretion of cell-cycle-associated proteins cyclin A and B1 [23]. The clinical implication of these findings was studied in two prospective trials evaluating mucositis as the primary endpoint for patients receiving RT for HNSCC. No statistically significant differences were seen between morning and evening treatments, 38% vs. 26% (p = 0.08) in the Indian cohort and 52.9% vs. 62.4% (p=0.17) in the Canadian cohort.[24,25]. Likewise, Elicin et al did not find an effect of treatment time on tumor control or on toxicity, and this was not tested in our current study because data were not available.

The main limitation of this study is its retrospective nature, with data on treatment time and treatment duration not specifically collected as they were not of interest in the original meta-analyses. Nevertheless, mid-treatment time and corresponding season was available for the majority of the subjects, and one of the strengths of this study is the availability of data from a large number of countries, in particular Northern countries where differences were expected to be more pronounced. Furthermore, the season of diagnosis or treatment inherently cannot be randomized in prospective trials, and the utilization of these two large multi-institutional databases likely eliminated selection bias. Even if effects have been found in preclinical studies, these are likely not translated in the clinical setting. Significant prognostic factors found in this study are consistent with current knowledge: sex, tumor site, and tumor stage [26–28].

Conclusion

The season of treatment delivery of RT was not seen to impact PFS or loco-regional failure in two large databases of non-metastatic HNSCC. We could not confirm the findings from the single center retrospective study of Elicin et al, which is possibly a false positive result.

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