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Abstract

Background: The onset of the coronavirus disease 2019 (COVID-19) outbreak caused major interruptions to the entire healthcare network affecting referral, diagnosis and treatment pathways with the potential to affect cancer treatment outcomes. In Ireland a national lockdown was initiated in March 2020 involving a stay-at-home order with a limitation on travel, social interactions and closure of schools, universities and childcare facilities. We designed a retrospective study comparing treatment outcomes for patients with oropharyngeal cancer treated before and during the COVID pandemic.

Materials and methods: All patients receiving radical radiotherapy for oropharyngeal cancer pre-COVID (July 17 – July 18) and during COVID (Mar 20 – Mar 21) were included. Patient and disease characteristics, diagnostic timelines, treatment delays and disease outcomes were extracted from the patient record. Disease free survival and overall survival were calculated for both groups.

Results: 159 oropharynx patients were included, 76 in the pre-COVID group (Group 1) and 83 in the pandemic group (Group 2). When comparing Group 1 and 2, respectively:

There were no differences in human papilloma virus (HPV) status (74% *vs.* 71% p = 0.795) or Tumour–Node–Metastasis (TNM) overall stage [American Joint Committee on Cancer

(AJCC) ed. 8]: (Stage 1: 25% *vs.* 45.8%, Stage 2: 28.9% *vs.* 18.1%, Stage 3: 21% *vs.* 15.7%, Stage 4: 25% *vs.* 20.5%, p = 0.268). Use of moderate hypofractionated regime increased during the pandemic (2.6% to 10.8%) and one patient omitted chemotherapy due to COVID-related reasons. There was no change in overall treatment times between groups with COVID-related sepsis accounting for one significant delay and one death during treatment.

Overall survival at 2 years via Kaplan-Meier analysis; Group 1 cumulative proportion surviving at 2 years was 77% [95% confidence interval (CI): 67–86%] *vs.* 85% in Group 2 (95% CI: 77–93%, p = 0.35). The disease free survival at 2 years was 69% in Group 1 (95% CI: 59–80%) *vs.* 76% in Group 2 (95% CI: 67–85%, p = 0.567).

Conclusion: In spite of challenges related to the COVID-19 pandemic, we have demonstrated that oropharyngeal cancer patients treatment standards and outcomes were maintained. We did not demonstrate any significant difference in overall survival and disease free survival at 2 years when compared to a similar group prior to the pandemic.

Introduction

The period following the widespread outbreak of the coronavirus disease 2019 (COVID-19) pandemic in early 2020 created a unique and unprecedented stress on healthcare systems across the world, requiring a rapid restructuring of all clinical pathways to meet the challenge. Local and national resources at all levels were repurposed or redeployed to create public health and clinical care structures to treat COVID-19. A national lockdown was commenced in Ireland in March 2020 requiring all citizens not defined as front line workers to stay at home, to remain within 2km of their home at all times and, if aged over 70 years, not to leave the house at all [1].

Prioritisation of COVID-19 related care including redeployment of staff towards treatment of COVID-19 infected patients in combination with temporary pausing of screening, diagnostic, medical and surgical oncology procedures resulted in significant impacts on most oncology patients care [2]. Head and neck cancer patients were a vulnerable group during this period. Flynn et al. [3] demonstrated that head and neck patients treated in 2020 were more likely to present with higher cancer stage, with longer associated preceding symptom duration with a higher risk of an emergency presentation.

The Irish National Cancer Control Programme published radiotherapy guidelines [4] suggesting prioritisation of curative treatment plans for category 1 diagnoses, temporary suspension of palliative radiotherapy treatments and deferral of radiotherapy treatments for 1–3 months in patients in specific cancer groups where a delay was deemed of minimal

clinical impact. These recommendations were rolled out on a phased basis, with services continuing as normal where treatment capacity was unaffected, but reducing in line with available resources where treatment capacity was reduced.

Changes to clinical care of head and neck cancer patients in the radiotherapy department included the use of virtual consultation, a ban on routine nasendoscopy and the use of more hypofractionated regimens to reduce the number of patient visits to the hospital.

There is a lack of published long-term outcome data for head and neck cancer patients treated during the pandemic. Kang et al. [5] and Venktasai et al. [6] demonstrated no difference in 6 month and 1 year outcomes, respectively, for a small group of head and neck cancer patients treated with radical radiotherapy during the pandemic. Schoonbeek [7] and Peacock [8] used large population based analysis of head and neck cancer trends prior to the pandemic to demonstrate a 25% drop-off in expected diagnoses during 2020 and a 2.4% decline in 1 year relative survival, respectively.

We designed a retrospective study to assess the impact of the COVID-19 lockdown in Ireland on outcomes for oropharyngeal cancer patients treated with curative intent radiotherapy in our institution.

Materials and methods

Patients reviewed for radical radiotherapy consultation with a diagnosis of new oropharyngeal cancer during 2 separate timelines were included in this study: Group 1 were assessed in a radiotherapy clinic in a 12 month period prior to the pandemic (July 2017–July 2018) and Group 2 were assessed during a 12 month period from the onset of lockdown in Ireland (March 2020–March 2021).

Inclusion criteria included: newly diagnosed non-metastatic oropharynx cancer, histologically confirmed squamous cell carcinoma. Exclusion criteria included: prior head and neck cancer diagnosis, any patient not suitable for curative intent treatment. Patient and disease characteristics were extracted retrospectively from the electronic patient record. Treatment delay was defined as any duration > 50 days for a 35 fraction regimen and any duration > 43 days for a 30 fraction regimen. Documented reasons for treatment gaps were recorded.

Statistical analysis

All statistical analyses were performed using SPSS v29. Independent t-test and chi-squared tests were used to establish any differences in the age, stage and human papilloma virus (HPV) status of patients at presentation. Overall survival (OS) and progression-free survival

(PFS) rates were calculated using the Kaplan-Meier method. Overall survival time period was defined as duration from final fraction of radiotherapy to death, and disease-free survival was defined as duration from final fraction of radiotherapy to recurrence. Follow up data was censored on 1st March 2023 for all survival outcome. Recurrence was confirmed by radiological or histological assessment.

This study was approved by the local research ethics board on 14th March 2023.

Results

Initial screening identified 89 patients in Group 1 of whom 13 (15%) were excluded and 97 patients in Group 2 of whom 14 (14%) were excluded after applying the inclusion and exclusion criteria. A total of 159 oropharynx patients were included, 76 in Group 1 and 83 in Group 2. Patient, disease and treatment characteristics are summarised in table 1. The median age was similar in both groups. There was a higher proportion of female patients in Group 1 (31% versus 12%). HPV related tumours accounted for 74% in group 1 and 71% in group 2 (p = 0.795). Tumour–Node–Metastasis (TNM) overall stage distributions [American Joint Committee on Cancer (AJCC) ed. 8] were as follows in Group 1 and 2, respectively: Stage 1: (25% vs. 45.8%), Stage 2: (28.9% vs. 18.1%), Stage 3: (21.1% vs. 15.7%), Stage 4:(25% vs. 20.5%). When grouped (with continuity correction) there was no statistically significant difference in overall stage (p = 0.268).

Use of moderate hypofractionated regime increased during the pandemic (2.6% to 10.8%). The rate of concomitant chemotherapy was 93.3% and 86.7% in group 1 and 2, respectively (p = 0.269). A single patient omitted chemotherapy due to patient and physician concerns regarding risk of COVID-19 related death due to underlying significant cardiorespiratory comorbidities. In group 1 there were 6 patients (7.8%) with unexpected delays vs. 5 patients (6%) in group 2. The reasons for delays were similar in both groups including need for replanning and medical illness. Of note, there was one Covid related treatment delay as the patient required temporary respiratory support during treatment. A single patient died during treatment due to Covid related illness: the patient completed 14 fractions of radiotherapy with concomitant cisplatin.

OS at 2 years (Fig. 1) in group 1 was 77% [95% confidence interval (CI): 67–86%) vs. 85% in group 2 (95% CI: 77–93%, p = 0.35). The disease free survival at 2 years (Fig. 2) was 69% in group 1 (95% CI: 59–80%) vs. 76% in group 2 (95% CI: 67–85%, p = 0.567). When assessing HPV associated oropharyngeal cancers in isolation, overall survival at 2 years was 87% in group 1 vs. 92% in group 2 (p = 0.213).

In terms of patient outcomes six patients were diagnosed with local/locoregional failure; three patients (4%) in Group 1 and three patients (4%) in Group 2. Of the three patients in Group 1, two patients received palliative chemotherapy and one received no salvage treatment due to poor fitness. In Group 2 two patients received salvage surgery in the form of neck dissection and one received palliative immunotherapy. Twenty-two patients were diagnosed with distant failure (six of whom had synchronous local failure) — fifteen patients (20%) from Group 1 and seven patients (8%) from Group 2. Of the fifteen patients in group 1, nine received palliative systemic treatment, two received palliative radiotherapy + systemic treatment, one received palliative radiotherapy alone and three received no salvage treatment. Of the seven patients in Group 2, two underwent salvage surgery followed by systemic treatment, one received systemic treatment alone, one received palliative radiotherapy + systemic treatment, one received palliative radiotherapy alone and two received no salvage treatment. A total of 13 patients were diagnosed with persistent disease following treatment via a combination of post treatment imaging and biopsy; six patients (8%) in Group 1 and seven patients (8%) in Group 2. Two patients were found to have persistent disease on post treatment imaging with synchronous distant metastases, both from Group 2 and both received palliative chemotherapy (one with immunotherapy). Five patients were suitable for salvage surgery in the form of neck dissection (two from Group 1 and three from Group 2). The remainder of this group were not suitable for surgery and assessed for suitability of palliative systemic treatment, three patients from Group 1 and one patient from Group 2 received palliative chemotherapy or immunotherapy. One patient from Group 1 and one patient from Group 2 were not suitable/fit for salvage treatment.

Discussion

Our study is the first looking at long-term outcomes of a large group of oropharynx cancer patients treated with curative radiotherapy during the COVID-19 pandemic. When comparing this group with a similar group of patients treated before the pandemic we demonstrated no significant difference in overall survival and disease free survival at 2 years. Our results demonstrated no significant difference in stage of cancer at presentation and we did not observe any increase in treatment delays encountered by patients during the pandemic.

Our results are similar to a number of smaller studies published to date. Venkatasai [6] assessed the outcomes of 25 head and neck cancer patients treated with curative intent radiotherapy during the pandemic and compared them to a similar group treated prior to the pandemic in a large Indian Oncology Centre. They noted an 8 day increase in the median

radiotherapy treatment duration but demonstrated no significant change in overall survival or disease free survival at 1 year follow-up. Kang [5] similarly demonstrated no difference in 6 month outcomes for a group of 38 oropharynx cancer patients treated during the pandemic with curative intent radiotherapy in a large American Oncology Centre despite increased use of telemedicine consultations during the pandemic. Peacock [8] used Belgian population based data from 2017–2019 to extrapolate trends in head and neck cancer incidence, clinical stage and 1-year relative survival and create expected values for 2020 and compare them to those observed. They noted a 2.4% decline in 1 year relative survival when comparing observed values with expected based on extrapolated data. Our results are among the first to demonstrate preservation of 2 year outcomes in the oropharynx cohort and highlight the important role of radiotherapy treatment during the pandemic [9].

Our study did not demonstrate any significant change in overall stage at presentation during a 12 month period from the commencement of national lockdown measures. We chose this timeline as we felt this was adequate to capture patients that may have been reluctant to present to hospital in the early stages of the pandemic. We noted a small reduction in stage 3 (21% Group 1: 15.7% Group 2) and stage 4 (25% Group 1: 20.5% Group 2) disease, and an increase in patients presenting with stage 1 disease (25% Group 1: 45.8% Group 2). Szewczyk [10], Heckel [11] and Cwinthal [12] similarly demonstrated no significant increase in the numbers of patients diagnosed with locally advanced disease during the pandemic. Our findings were in contrast to those of Flynn and Peacock which demonstrated worse overall stage of presentations during the pandemic. These noted differences are likely explained by the multifactorial nature of head and neck cancer presentations influenced by factors such as gender, smoking status, anatomical location of the cancer and dental review [13] and, thus, conclusions regarding the exact impact on oropharyngeal cancer presentations during the pandemic are challenging.

The National Cancer Registry Ireland (NCRI) published a 2022 report on the impact of the COVID-19 pandemic [14], estimating a shortfall of 15% in “mouth and pharynx” cancer rates in 2020 vs 2019. Additionally, it was noted that female patients were more susceptible to this shortfall, with a 22% drop-off in female patients versus 13% in males. Our study observed similar trends with a reduction in the proportion of females from 32% to 12%. This observation may suggest the female oropharynx group were more vulnerable to delayed presentations which have not been captured in our chosen timeline. To date there has been no robust published data to suggest female cancer patients have been more impacted by the pandemic than male patients. It is of interest to note women in the Irish population account

for 98% of full time carers [15] with almost twice as many unpaid female as male carers providing over 43 hours of care per week. During the pandemic voluntary caring services for the elderly stopped, further increasing the burden on female carers in Ireland, placing significant strain on the female population caring for people at home. Additionally, these women may have been fearful of presenting to hospital in case of contracting and spreading the virus to their patients or elderly family members making them vulnerable to delayed hospital presentation with a new cancer. We await longer term cancer registry data to fully understand the overall impact of the pandemic on oropharynx cancer patients outcomes and, in particular, the outcomes of female patients.

Our study demonstrated no significant change in the number of patients encountering radiotherapy prolongation during treatment. Despite the numerous challenges during the pandemic including patients contracting COVID-related illness during treatment, we observed a small relative decrease in the number of delays when compared to the 2019 cohort. We observed a small relative decrease in the numbers of patients undergoing concomitant chemotherapy with only one patient deemed unsuitable for chemotherapy due to COVID-related risks, the remainder of chemotherapy omissions were in keeping with treatment guidelines. Finally, we noted one Covid related death during treatment. These details highlight the positive impact of the national guidelines prioritizing head and neck cancer radiotherapy during the pandemic.

This study is one of the largest to date to assess the impact of the COVID-19 pandemic on oropharynx patients undergoing curative radiotherapy; however, we acknowledge a number of limitations of our study. Firstly, this was a retrospective analysis of a cohort treated in a large tertiary referral network; however, conclusions regarding trends in overall survival of this group may not be reflective of national or international trends. Secondly, regarding timelines assessed, we chose 12 months from the onset of the first national lockdown in order to capture potential late presentations of patients who may have been reluctant to attend hospital early in the lockdown timeline. Despite this choice, we observed a reduction in overall proportion of patients with locally advanced disease. This may suggest that the timeline was not adequate to sufficiently capture patients that experienced delayed presentation. Finally, owing to the diversity of lockdown measures across different countries around the world we would caution the relevance of our results when applied to international cohorts of oropharynx patients. Differences in time of lockdown commencement, duration and variations in strictness of restrictive measures had a significant impact on COVID-19

containment [16] and were likely to have impacted cancer patients behaviours during this time.

Conclusions

In spite of challenges related to the COVID-19 pandemic, this study has demonstrated that oropharyngeal cancer treatment standards and outcomes were maintained at 2 years in a large tertiary centre.

Conflicts of interest

The authors whose names are listed above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Data sharing statement

Raw data were generated at St Luke's Radiation Oncology Network Dublin, Ireland for review. Derived data supporting the findings of this study are available from the corresponding author [Dr Niall O'Dwyer] on request.

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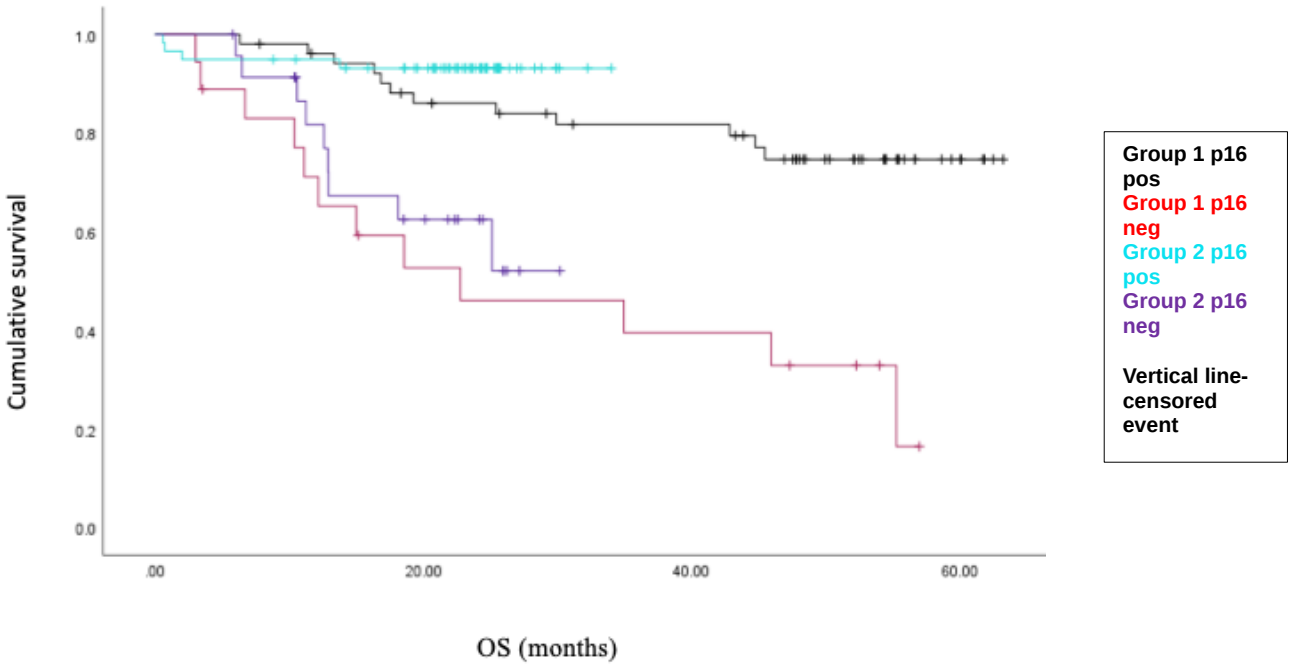

Figure 1. Overall survival (OS) Kaplan Meier assessment

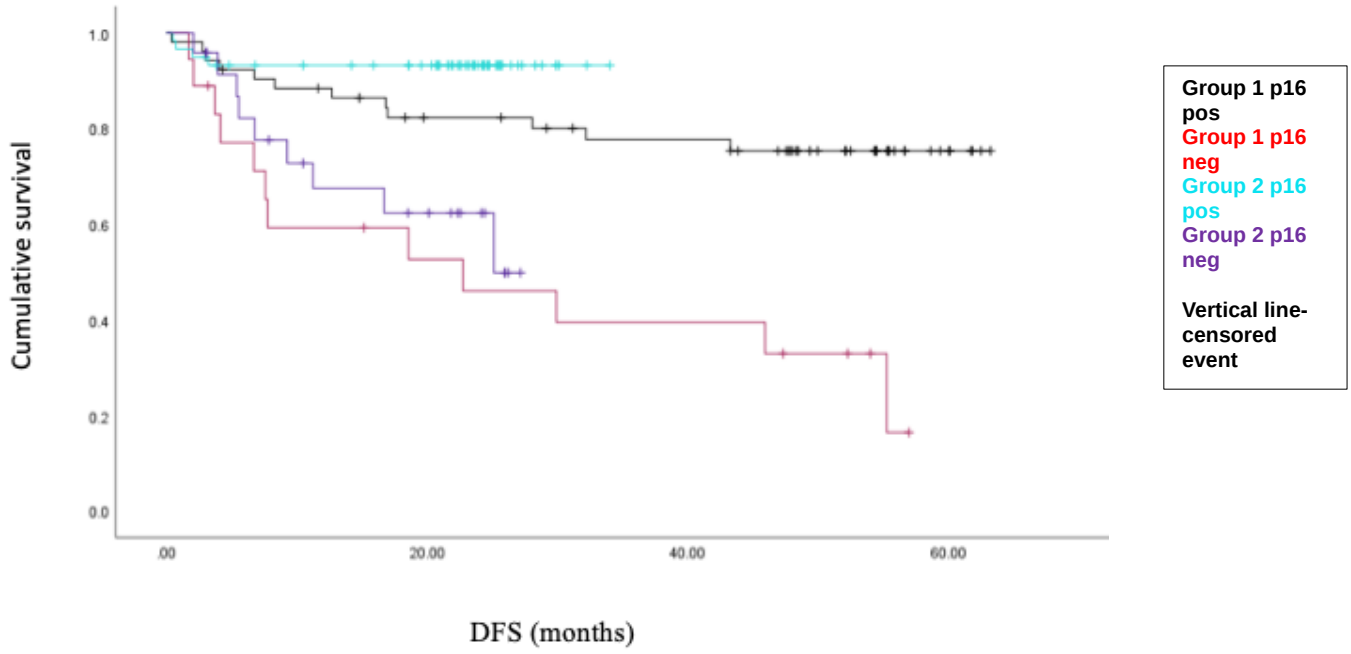

Figure 2. Disease-free survival (DFS) Kaplan Meier assessment

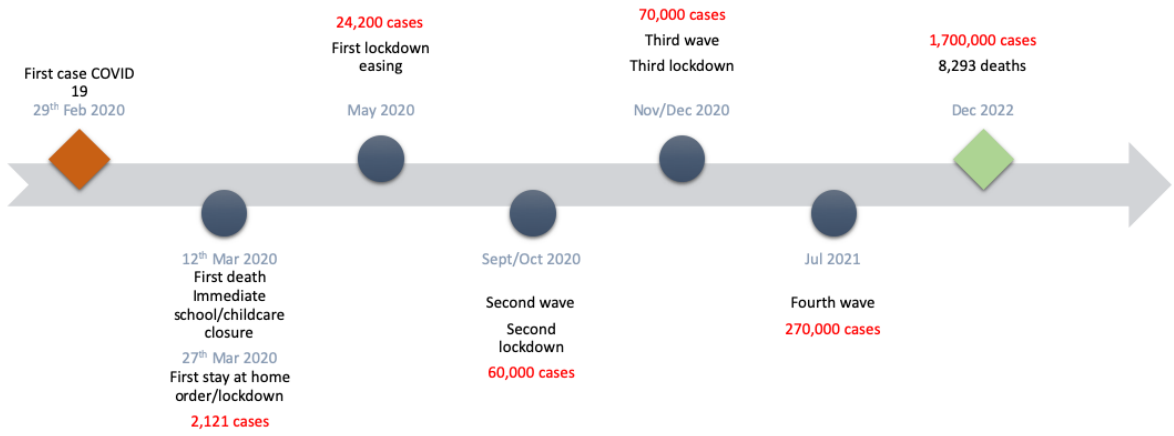

Figure 3. COVID-19 timeline in Ireland 2020–2022 (lockdown, case numbers in red)

Table 1. Group characteristics summary: Group 1: 2017–2018, Group 2: 2020 COVID-19 Lockdown: 2021

	Group 1 **N = 76 (%)**	**Group 2** **N = 83 (%)**	**p-value**

Sex, n (%)			
Male	52 (68.42%)	73 (87.9%)	**0.003**
Female	24 (31.58%)	10 (12.04%)	
Age at diagnosis, Median (range) [yrs]	59 (27–82)	59 (36–83)	**0.498**
P16/HPV status			
Positive, n (%)	52 (68%)	59 (71%)	**0.795**
Unknown	6 (8%)	0 (0%)	
Tumour characteristics			
T stage			
Tx	2 (2.6%)	2 (2.4%)	
T1	11 (14.5%)	9 (10.8%)	
T2	22 (28.9%)	41 (49.4%)	
T3	24 (31.6%)	19 (22.9%)	
T4	17 (22.4%)	12 (14.5%)	
N stage			
N0	4 (5.3%)	13 (15.7%)	
N1	35 (46.1%)	48 (57.8%)	
N2	30 (39.5%)	20 (24.1%)	
N3	7 (9.2%)	2 (2.4%)	
Overall stage, n (%)			
1	19 (25%)	38 (45.8%)	**0.268 (grouped*)**
2	22 (28.9%)	15 (18.1%)	
3	16 (21%)	13 (15.7%)	
4a	16 (21.1%)	17 (20.5%)	
4b	3 (3.9%)	0 (0%)	
Treatment details			
Radiotherapy dose, n (%)			
	73 (96.1%)	74 (89.2%)	
70 Gy/35 fr	2 (2.6%)	9 (10.8%)	
65 Gy/30 fr	1 (1.3%)	0	
55 Gy/20 fr			
Radiotherapy treatment duration, days (median)	48	48	
Unplanned treatment	6 (7.8%)	5 (6%)	

delays, n (%)			
Concomitant chemotherapy, n(%)	71 (93.3%)	72 (86.7%)	**0.269**
Chemotherapy regimen	Cisplatin: 54 (76%) Carboplatin: 14 (20%) Cetuximab: 2 (3%) Induction cisplatin/5-fluorouracil: 1 (1%)	Cisplatin: 61 (85%) Carboplatin: 6 (8%) Carboplatin/5-fluorouracil: 4 (6%) Carboplatin/paclitaxel: 1 (1%)	
Median follow up [mo]	48	23	

*Stages grouped for statistical assessment: Stage 1 + 2 and Stage 3 + 4.