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Impact of antibiotic use during curative treatment of locally-advanced head and neck cancers with chemotherapy and radiotherapy.

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Abstract:	Background: Pre-clinical evidence suggests reduced efficacy of anticancer treatment in patients exposed to broad-spectrum antibiotics. It is hypothesised that this phenomenon may be explained by the effects of antibiotics on the composition of the microbiota. To assess this in a clinical setting, we analysed the impact of antibiotics in patients with locally-advanced head and neck cancer (LAHNC) treated with curative intent with chemotherapy and radiotherapy. Material and Methods: Retrospective data for LAHNC patients treated with curative intent (245 induction chemotherapy followed by chemoradiation, 17 surgery followed by postoperative chemoradiation, 6 chemoradiation, 3 radiotherapy alone and 1 radiotherapy with concurrent cetuximab) were analysed. We evaluated the impact of antibiotics prescribed during primary anti-cancer treatment on progression-free (PFS), overall (OS) and disease-specific survival (DSS) rates by multivariate Kaplan-Meier and Cox proportional hazards regression analysis. Results: Among 272 patients, those receiving antibiotics between within 1 week before and 2 weeks after treatment (N = 124) progressed significantly earlier and had lower OS and DSS rates. In the multivariate analysis, administration of antibiotics was independently associated with reduced PFS (HR 1.98, P=0.001), OS (HR 1.85, P=0.001) and DSS (HR 1.95, P=0.004). This effect was maintained with independence of reason for prescription, type and time of antibiotic prescription. The negative impact was greater for patients who received 2 or more courses of antibiotics. Antibiotic treatment was correlated with increased risk of loco-regional relapse. Conclusions: Our data suggest a negative impact of antibiotic therapy on treatment outcomes following chemoradiation with curative intent in patients with LAHNC. This potential harm should be considered when prescribing broad-spectrum and prophylactic antibiotics for such patients.
Suggested Reviewers:	

12th February 2020
Editorial Department of European Journal of Cancer

Dear Dr Jean-Pascal Machiels,

I am submitting a manuscript for consideration of publication in the European Journal of Cancer. The manuscript is entitled " Impact of antibiotic use during curative treatment of locally-advanced head and neck cancers with chemotherapy and radiotherapy".

It has not been published elsewhere and that it has not been submitted simultaneously for publication elsewhere.

With the field of microbiota research rapidly moving, emerging interest has arisen in investigating the role of antibiotics and anti-cancer treatment efficacy. In this retrospective study that included 272 patients with locally-advanced head and neck cancer treated with chemotherapy and radiotherapy, we found that antibiotic treatment administered during the oncologic treatment was associated with significantly worse overall survival and a higher risk of local relapse. We hypothesize that alteration of the microbiota of the upper aerodigestive tract by antibiotics may have impact on tumour radiosensitivity and, hence, outcome in locally-advanced head and neck cancers.

I hope the manuscript will turn out to be valuable as so far not many studies have investigated the role of antibiotics and their impact in the outcome for head and neck squamous cell carcinomas.

Yours Faithfully,

Dr Pablo Nenclares

Clinical Researcher
Head and Neck Unit
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European Journal of Cancer
Author Form

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Title of Manuscript:

IMPACT OF ANTIBIOTIC USE DURING CURATIVE TREATMENT OF LOCALLY-ADVANCED HEAD & NECK CANCERS WITH CHEMOTHERAPY AND RADIOTHERAPY

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Signed (corresponding author): .....
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HIGHLIGHTS

- Microbiota changes may have a role on anti-cancer treatment efficacy.
- Antibiotics during the oncologic treatment associated with worse survival in HNSCC.
- Antibiotic treatment correlated with increased risk of loco-regional relapse.

TITLE PAGE

Impact of antibiotic use during curative treatment of locally-advanced head and neck cancers with chemotherapy and radiotherapy.

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ABSTRACT

Background: Pre-clinical evidence suggests reduced efficacy of anticancer treatment in patients exposed to broad-spectrum antibiotics. It is hypothesised that this phenomenon may be explained by the effects of antibiotics on the composition of the microbiota. To assess this in a clinical setting, we analysed the impact of antibiotics in patients with locally-advanced head and neck cancer (LAHNC) treated with curative intent with chemotherapy and radiotherapy.

Material and Methods: Retrospective data for LAHNC patients treated with curative intent (245 induction chemotherapy followed by chemoradiation, 17 surgery followed by postoperative chemoradiation, 6 chemoradiation, 3 radiotherapy alone and 1 radiotherapy with concurrent cetuximab) were analysed. We evaluated the impact of antibiotics prescribed during primary anti-cancer treatment on progression-free (PFS), overall (OS) and disease-specific survival (DSS) rates by multivariate Kaplan-Meier and Cox proportional hazards regression analysis.

Results: Among 272 patients, those receiving antibiotics between within 1 week before and 2 weeks after treatment (N = 124) progressed significantly earlier and had lower OS and DSS rates. In the multivariate analysis, administration of antibiotics was independently associated with reduced PFS (HR 1.98, P=0.001), OS (HR 1.85, P=0.001) and DSS (HR 1.95, P=0.004). This effect was maintained with independence of reason for prescription, type and time of antibiotic prescription. The negative impact was greater for patients who received 2 or more courses of antibiotics. Antibiotic treatment was correlated with increased risk of loco-regional relapse.

Conclusions: Our data suggest a negative impact of antibiotic therapy on treatment outcomes following chemoradiation with curative intent in patients with LAHNC. This potential harm should be considered when prescribing broad-spectrum and prophylactic antibiotics for such patients.

INTRODUCTION

Head and neck cancer accounts for more than 650,000 cases of malignancy worldwide. Many patients are diagnosed with locally-advanced disease and chemoradiation (CRT) is a treatment-of-choice. However, radiotherapy (RT) and CRT can be associated with a number of acute toxicities that may require antibiotic treatment. The majority of antibiotics prescribed in this setting have broad-spectrum activity and have the potential to alter the normal microbiota.

Recent research has highlighted the importance of a patient's microbiota in the pathogenesis and therapeutic response of a number of diseases, including cancer [1], [2]. A number of studies have implicated changes in the bacterial microflora in cancer pathogenesis, chemotherapy metabolism, drug- and radiation-induced toxicities and the efficacy of anti-CTLA4 and anti-PD-1/PDL-1 cancer therapies [3]–[7]. Recent evidence suggests a link between administration of antibiotics targeting gram-positive pathogens, composition of the gut microbiota and efficacy of anti-cancer treatment in mice [8]-[10].

As yet, it remains unclear whether these findings are applicable to humans. Pflug et al. reported on patients treated with cyclophosphamide as first-line therapy for chronic lymphocytic leukaemia and a cisplatin-containing regimen for relapsed lymphoma and showed that antibiotic treatment was an independent adverse factor for response, progression-free (PFS) and overall survival (OS) [11].

Therefore, in this retrospective study, we sought to examine the impact of antibiotic therapy on treatment outcomes following curative-intent chemotherapy and radiotherapy in patients with locally-advanced head and neck cancer (LAHNC).

MATERIAL AND METHODS

Patients

Data were retrospectively collected from prospective cohorts of previously published studies from our own single institution [12]–[14]. Studies were approved by Research Ethics and local R&D committees. Patients were eligible for inclusion if they were diagnosed with stages III and IVA/B and treated with curative intent comprising one of the following regimens: IC followed by concurrent CRT, definitive CRT alone or surgery followed by RT with or without concurrent chemotherapy. We excluded patients without available information on concomitant medications. A total of 272 patients diagnosed with LAHNC from March 2001 to February 2010 were included.

As per Royal Marsden Hospital protocol, patients treated with IC received 2 cycles consisting of cisplatin (100 mg/m^2) or carboplatin (AUC5) on day 1 followed by a 24-hour intravenous infusion of 5-fluorouracil (1,000 mg/m^2) for 4 days, every 21 days. IC was followed by RT (65 Gy in 30 fractions) with 2 cycles of concurrent cisplatin (100 mg/m^2) or carboplatin (AUC5) on days 1 and 28. Patients who had undergone prior surgery received post-operative RT (65 Gy if R1/R2 resection or 60 Gy if R0) with or without concurrent chemotherapy (if R2 resection and/or extranodal extension). One patient received concurrent cetuximab.

The following variables were recorded: gender, age, primary site, TNM staging (7th edition), oncologic treatment duration, antibiotics prescribed, type, reason and date of prescription. Antibiotic administration was recorded if it occurred within 1 week before and 2 weeks after completing radiotherapy. Outcomes assessed were PFS, OS and disease-specific survival (DSS). The data were obtained from the electronic patient records. Informed consent for retrospective analysis was obtained at diagnosis.

Statistical analysis

We presented patients characteristics as means or frequency and used chi-square test for analysis of proportion across groups. We repeated the data balance analysis after propensity score weight adjustment. The prognostic impact of the administration of antibiotics was evaluated applying the Kaplan-Meier methodology, log-rank test and Cox proportional hazards regression analysis. PFS, OS and DSS were calculated from diagnosis to disease progression or death. Subjects without documented event for PFS, OS and DSS were censored at date of last information. We supplemented standard multivariate analyses using Cox model after implementing propensity-

score weight. All statistical tests were two-sided and statistical significance was defined by a *P* value less than 0.05. The analyses were performed with Stata V14.0.

RESULTS

Median age was 57 (range 26-86) years and 77% were male. Patient characteristics by antibiotic treatment are detailed in Table1. The most frequent primary site was the oropharynx (60.7%), followed by the hypopharynx and larynx. The majority of the patients had stage IVA disease (69.1%) and most were treated with IC followed by platinum-based CRT (85%). A total of 124 patients (45.6%) received antibiotics. All patients had performance status of 0 or 1. The reasons for antibiotic prescription were: for treatment of established dental infection during standard pre-radiotherapy preparation (34.7%); chest infection (16.9%); super-imposed bacterial infection of RT-induced dermatitis (5.7%) and mucositis (4%). Of note, in 34 patients (27.4%) the indication for antibiotic prescription was not clearly documented. The most common antibiotics prescribed were penicillin and derivatives (68.6%), followed by macrolides (20.5%) and quinolones (10.5%).

After balancing data using propensity-score-weight, there were no significant differences in the distribution of age, gender, staging and treatment between patients who did and did not receive antibiotics. We found a statistically significant lower proportion of patients with nasopharyngeal cancer in the antibiotic group (eTable1).

With a median follow-up of 54 months and median follow-up for survivors of 83 months, 95 developed disease recurrence (59 loco-regional relapse, 36 distant metastases and 9 combined loco-regional and distant recurrence) and 131 patients died. Median OS was 102.3 months; with 2- and 5-year estimated OS rates of 71.9 and 51.3%, respectively. Median PFS was not reached and 2- and 5-year estimated PFS rates were 72.2 and 62.9%, respectively. None of the patients died due to infective complications during treatment. A total of 77 patients died from the original cancer during follow-up, yielding 2- and 5-year DSS rates of 71.8% and 64.3%, respectively.

On univariate analysis, patients who had received antibiotics progressed significantly earlier (median PFS 147.8 months) compared to patients in the no-antibiotic group (median PFS not reached, P=0.0008) (Fig. 1A). OS was significantly lower in patients who had received antibiotics (median OS 71.9 months vs. 132 months, P=0.0007; Fig.1B). Moreover, patients in the antibiotic group had statistically lower DSS rates (2-year DSS 85% vs 68% and 5-year DSS 77.5% vs 61.8%, P=0.0026) (Fig1C).

On multivariate analysis including other relevant confounding factors (age, sex, stage, primary and nodal status, anti-cancer treatment and location), antibiotics remained an independent prognostic factor for PFS (HR 1.98,

95%CI 1.31-3, *P*=0.001), OS (HR 1.85, 95%CI 1.3-2.63, *P*=0.001) and DSS (HR 1.95, 95%CI 1.23-3.1, *P*=0.004). In addition, other prognostic factors for worse survival were: >65 years, T and N stage, other locations (unknown, oral cavity and sinuses) and IC (eTable2).

On multivariate Cox regression using propensity-score-weight including variables potentially associated with antibiotic therapy, the negative effect of the antibiotics was maintained for PFS (HR 1.87, 95%CI 1.2-2.9, *P*=0.005), OS (HR 1.7 95%CI 1.19-2.47, *P*=0.005) and DSS (HR 2.06, 95%CI 1.26-3.37, *P*=0.004) (eTable3, eFigure1).When repeating the analysis in the largest subgroup (oropharynx treated with IC, n=142), the prognostic association of antibiotics remained unchanged (eFigure2).

The negative impact on outcomes associated with antibiotics was maintained with independence of the time of antibiotic prescription (during IC vs. RT) and type of antibiotic (penicillin vs. other) (eFigure3, 4). The association of antibiotics with worse OS and DSS was independent to the reason of prescription (dental vs. no dental infection). However, the association between antibiotics prescribed for dental infection and PFS was not statistically significant (eFigure5). We analysed the pattern of recurrence, finding a statistically significant correlation between antibiotic use and loco-regional relapse but not between antibiotics and distant metastases (eFigure6).

To account for potential bias due to RT delays resulting from infective complications, we found no relationship between antibiotic prescription and delay in completion of RT (median length of 41 days for each group –range 25-56 days in the no-antibiotic and 37-53 days in the antibiotic group, *P*=0.212).

We performed a post-hoc sub-group analysis to identify patients who had received 2 or more courses of antibiotics (n=36). The negative impact on the oncologic outcome was even greater, with a statistically significant reduction of the PFS (2-year-PFS 78.7% if no antibiotics vs. 69.8% if 1 course vs. 50% if $\geq$2 courses, *P*=0.0043), the OS (2-year-OS 78.3%, vs. 70.8% vs. 46.8%, *P*=0.0007) and the DSS (2-year-DSS 84.8, vs. 75% vs. 50.5%, *P*=0.0009) (Figure2).

DISCUSSION

In this study we assessed the influence of antibiotic use on the outcome of RT or CRT as curative treatment for LAHNC. While previous studies have investigated the role of antibiotics on outcomes for hematologic tumours, there are very few data available on patients with solid tumours treated with curative-intent. We found that almost half of patients received antibiotics during the course of their anti-cancer treatment. Interestingly, the most common indication for prescription of antibiotics in this population was for issues related to the patients' dentition. We identified treatment with antibiotics as an independent risk factor for significantly reduced PFS, OS and DSS. Antibiotic use was significantly correlated with a pattern of local and regional relapse rather than distant recurrence. In addition, we found that the negative impact in outcomes was greater in patients who had 2 or more courses of antibiotics. Although this subgroup of patients who received several courses of antibiotics may represent the population with poorer treatment tolerance, the effects of antibiotics on the key survival measures was maintained when comparing patients who did not receive antibiotics and patients with just one antibiotic prescription. This led to the conclusion of an increasing negative prognostic impact of antibiotic use, regardless of the reason and time of prescription and the type of antibiotic.

Relatively little is known about whether and how the microbiota regulates the response to RT. However, since the gut microbiota can impact the immune response induced by immunogenic cell-death in both chemotherapy and immunotherapy [8],[9],[15], it seems reasonable to hypothesize that microbiota might influence the immunostimulatory effects of RT. In regard to RT-induced toxicities, it has been suggested that changes in the composition of the microbiota at epithelial surfaces might contribute to the pathogenesis of oral mucositis, diarrhoea, enteritis, colitis and bone marrow failure in both mice and patients treated with RT [16]. Indeed, although there is conflicting evidence on the use of probiotics, some studies have shown it to be beneficial in preventing RT- and chemotherapy-induced side effects. [17],[18]. In our study, the use of antibiotics was correlated with a pattern of increased loco-regional relapse rather than distant metastases, which raises the question whether specific changes in the oral microbiota may trigger the development of local relapse. Sonalika et al showed that, as compared to healthy individuals, patients diagnosed with oral squamous cell carcinoma, showed a different oral microbiota composition [19]. Interestingly, Crawford et al's investigations with germ-free mice treated with gamma-irradiation showed the importance of gut microbiota in conferring radiosensitivity to the small intestinal endothelium [7]. Our current findings raise the question as to whether the upper aerodigestive tract microbiota influences the response to treatment and disease course. We hypothesize that

alteration of the microbiota of the upper aerodigestive tract by antibiotics may have impact on tumour radiosensitivity and, hence, outcome in LAHNSCC.

One might argue that comorbidities, polypharmacy, concomitant medication and oncologic treatment could have dictated the use of antibiotics and, therefore, exerted an effect on outcomes. However, a number of objective findings from the current study argue against this hypothesis. First, all the patients had performance status of 0 or 1. We have not attempted to compare outcomes in those with performance status 0 versus 1 because all patients were judged to be sufficiently fit to withstand platin-based CRT. Second, the survival results documented in our study are in line with previously reported series [20] and the IC and intensity of concurrent chemotherapy regimen was the same in all patients with the exception of one subject who received concurrent cetuximab and, after balancing data using propensity-score-weight, there were no significant differences in the distribution by treatment. Although interaction between antibiotic prescription and early discontinuation or delays in anti-cancer treatment due to infectious complications was a potential confounder, no withdrawal of treatment was seen, and prolongation of RT was not related to infectious complications. In addition, in view of the propensity-score-weights regression results, we do not think that selection biases have affected our conclusions. None of the patients included in this analyse were HIV-positive or had any other known immunosuppressive state.

We acknowledge that a limitation was the lack of availability regarding the reason for antibiotic prescription in 33 patients and other potential confounders which were not analysed such as toxicity, HPV-status and comorbidities. However, to the best of our knowledge we have excluded the likelihood that our findings reflect nothing other than a systematic difference between the treatment groups based around unknown factors. Given HPV-testing was not widely applied at the time that this cohort was treated, this question will have to be addressed in future prospective studies.

While we indirectly assessed the changes of the composition of bacterial microflora by focusing on antibiotics, we could not establish a clear cause–effect relationship in the absence of an accompanying microbiome analysis. Further efforts, including faecal and/or oral microbiome analyses, should be made to reproduce our findings and deepen the knowledge of the underlying pathological mechanisms.

Nevertheless, our results, in line with pre-clinical research and some clinical data, can be considered strong enough to warrant some conclusions. First, since the potential negative impact of antibiotic treatment has been related to modification of gram-positive bacteria, the use of broad-spectrum antibiotics should be restricted

where possible. While the general value of empiric treatment is undisputed, more differentiated strategies such as antibiotic selection guided by antimicrobial susceptibility testing is highly recommended. Second, prophylactic antibiotics should not be routinely prescribed without careful consideration. A randomized controlled trial by Wijers at al. did not find any benefit of using antimicrobial treatment for selective oral decontamination over placebo in reducing oral mucositis [21]. In addition, as recommended by a recent review, treatment with systemic antibiotics for oral mucositis should be used judiciously and a swab from the oral mucosa for bacterial culture and sensitivity should be obtained so that antimicrobials can be tailored accordingly [22]. A recently published phase 2 trial showed that prophylactic antibiotic treatment with amoxicillin/clavulanic acid reduced hospitalisation rates and tended to be cost-effective [23]. However, it failed to show a reduction in the incidence of pneumonia. Additionally, long-term effects on resistance, outcomes and related costs are unknown. Indeed, the risk of inducing bacteria with antibiotic resistance is a challenge that exists alongside any possible impact on treatment outcomes from creating an antibiotic-altered microbiome. Therefore, as discussed by Nerina et al [24], the suggestion in LAHNC is not to overexpose patients to antibiotics, but this does not equate to denying the benefits of antibiotic therapy in the context of active infections. In the era of immunotherapy, it is likely that judicious antibiotic usage will be increasingly important; as several studies have confirmed that microbiome has a key role both on treatment response and prognosis [25].

The field of microbiota research is rapidly evolving, and manipulating the microbial population with the aim of reducing systemic toxicity and promoting anticancer therapy has become a hot topic of research [26]. In line with our results, further elucidation of those bacterial species hypothesized to modulate the efficacy of the CRT may be the first step towards development of a targeted bacteriotherapy, designed to supplement the microbiota during or after indispensable courses of antibiotic treatment.

CONCLUSIONS

While we identified antibiotics as an independent adverse factor for PFS, OS and DSS, further validation studies should be performed. Healthcare professionals should carefully consider these potential harms when prescribing antibiotics for LAHNC. Broad spectrum and prophylactic antibiotic prescriptions are particularly unlikely to have favourable risk benefit profiles. Further research in targeting microbiota changes in cancer is likely to become one of the next frontiers for precision and personalized medicine.

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DISCLOSURE

The authors declare no conflicts of interest.

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Figure 1. Kaplan-Meier survival curves for PFS (A), OS (B) and DSS (C) by antibiotic (ATX) prescription. Level of significance *P*<0.05.

Figure 2. Kaplan-Meier survival curves for PFS (D), OS (E) and DSS (C) by 1 or ≥2 courses of antibiotic (ATX) prescription. Level of significance *P*<0.05.

Figure1

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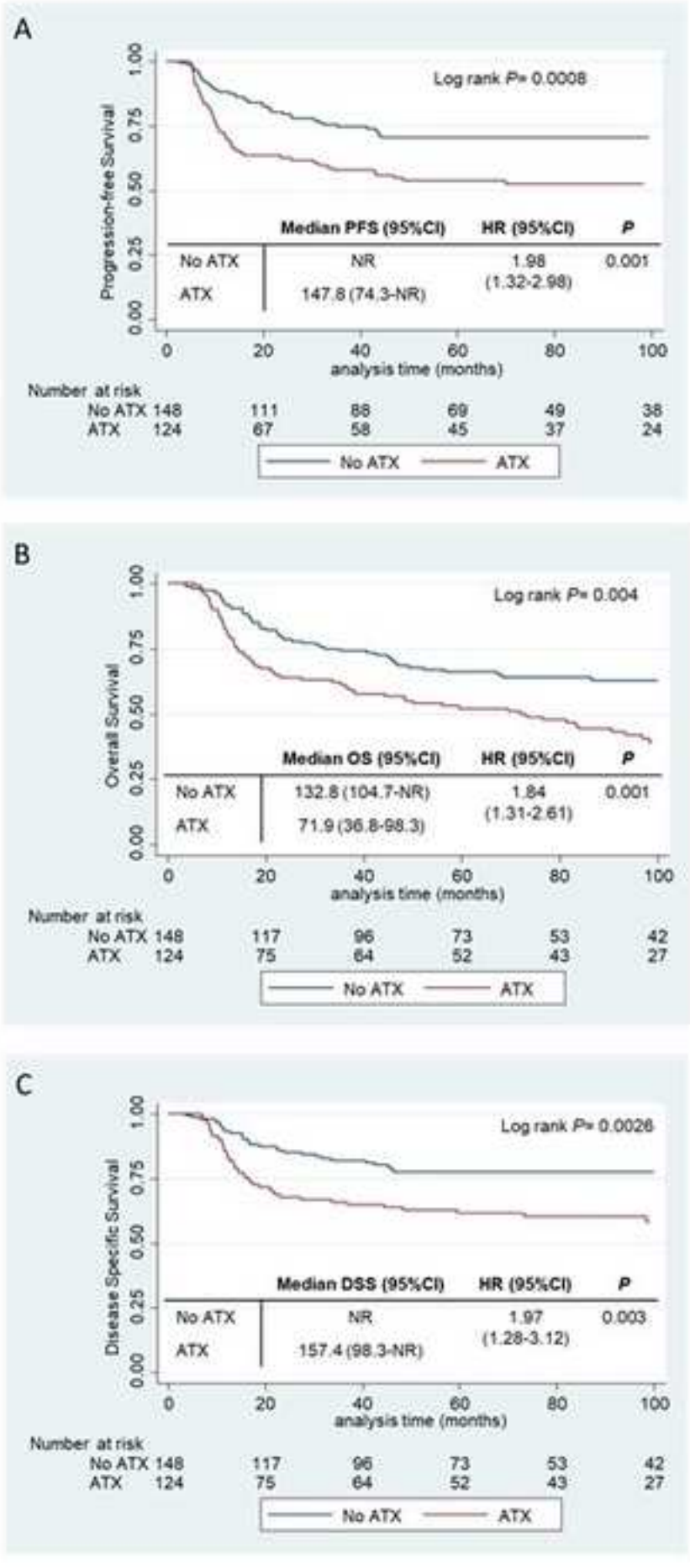

Figure2

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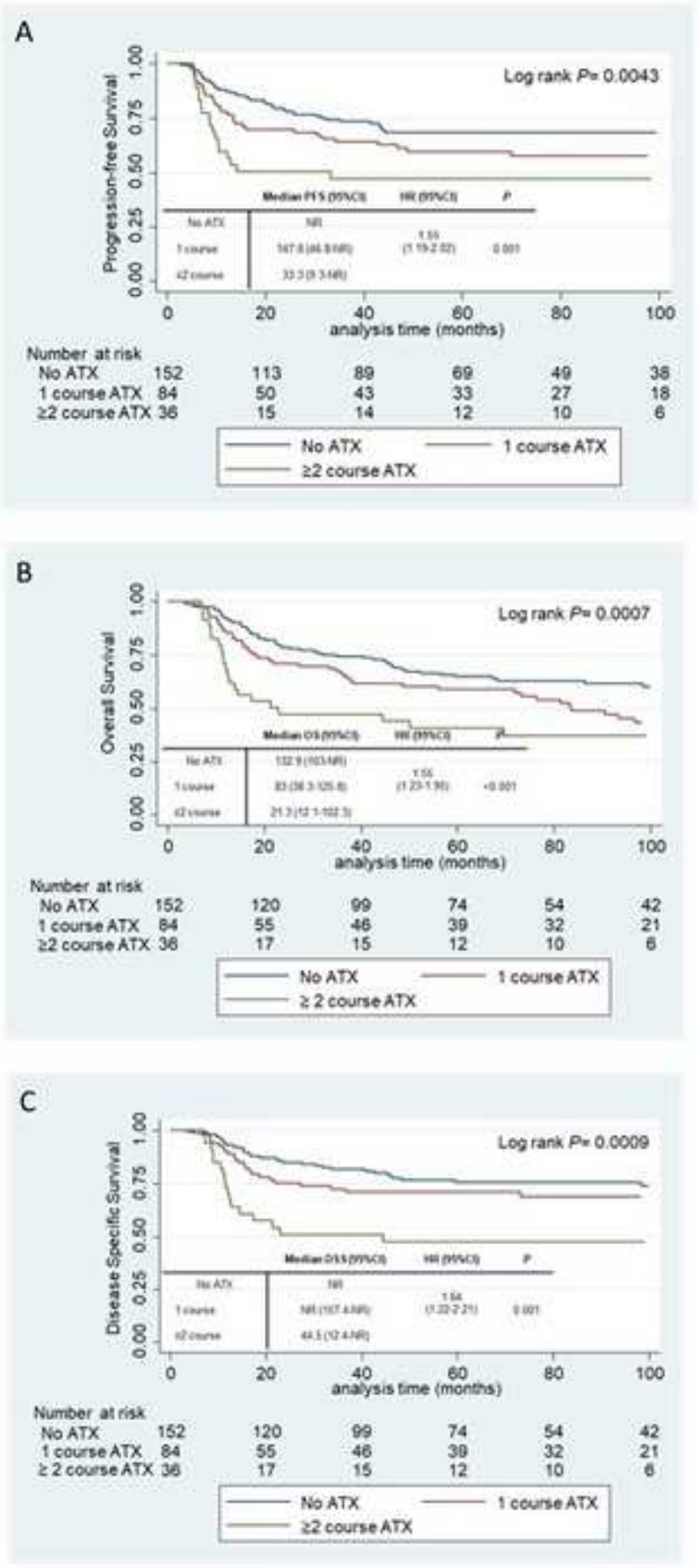
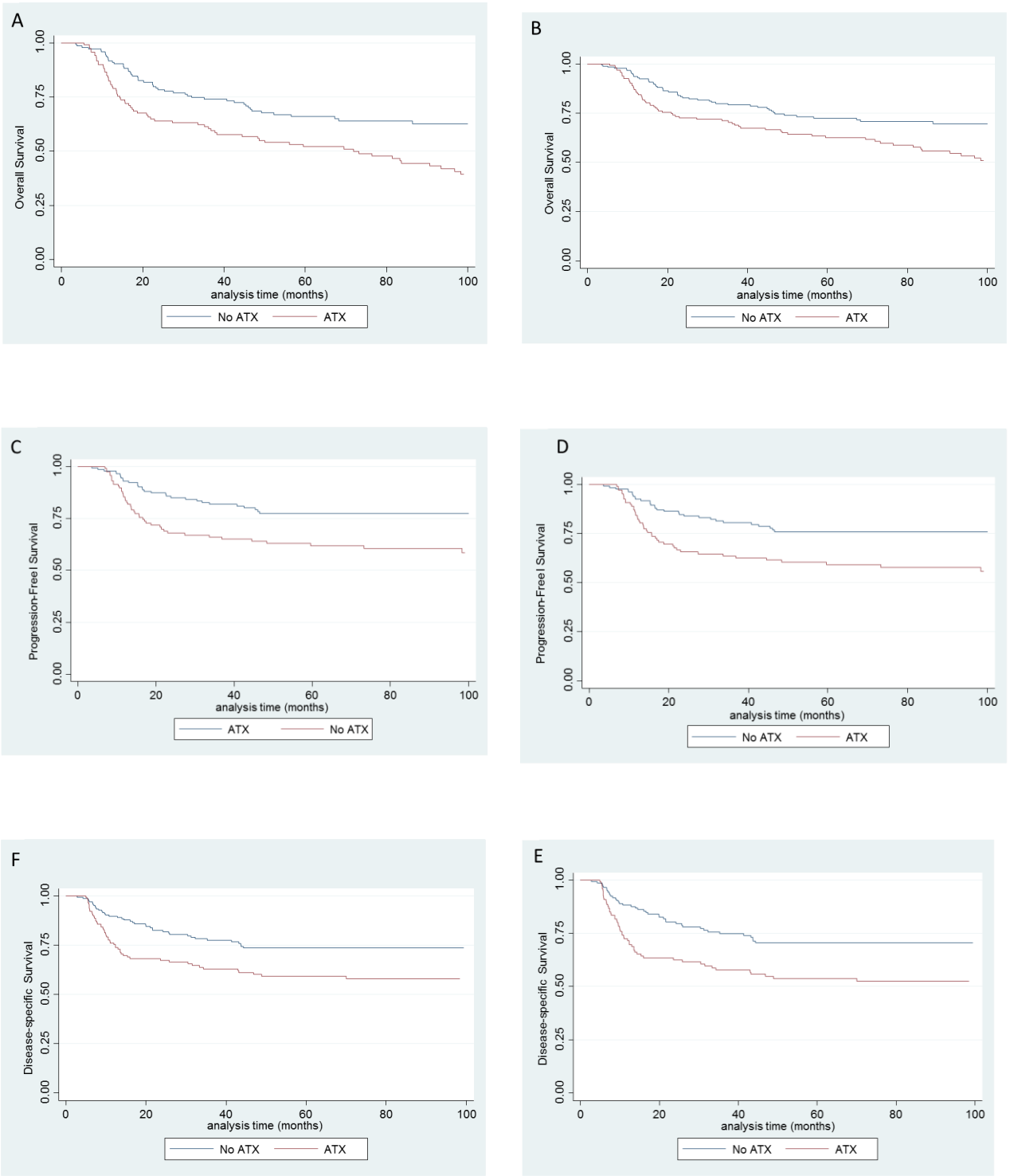


Declarations of interest

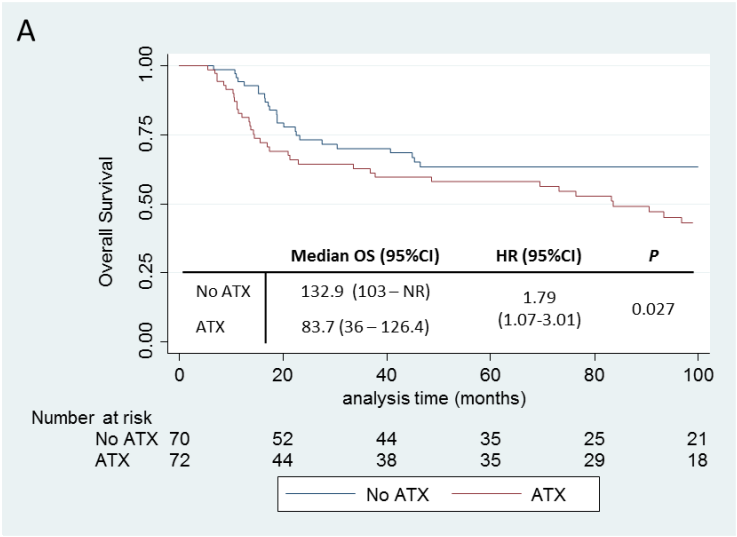
None

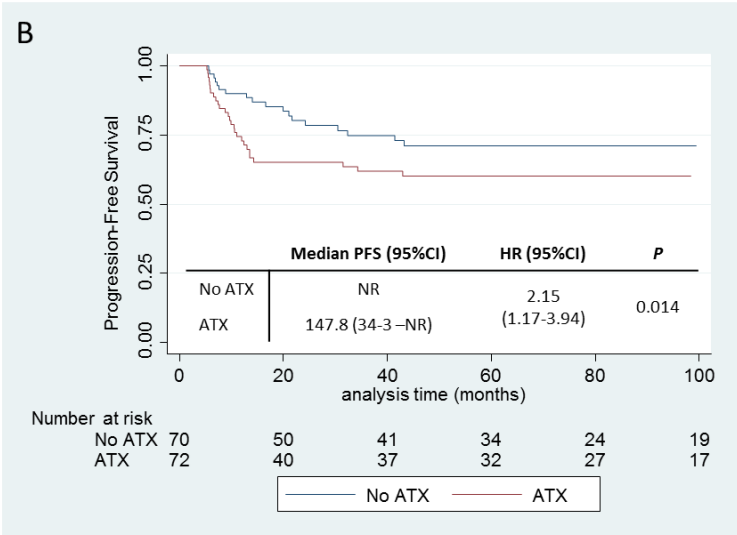
Supplementary Figure (online publication only)

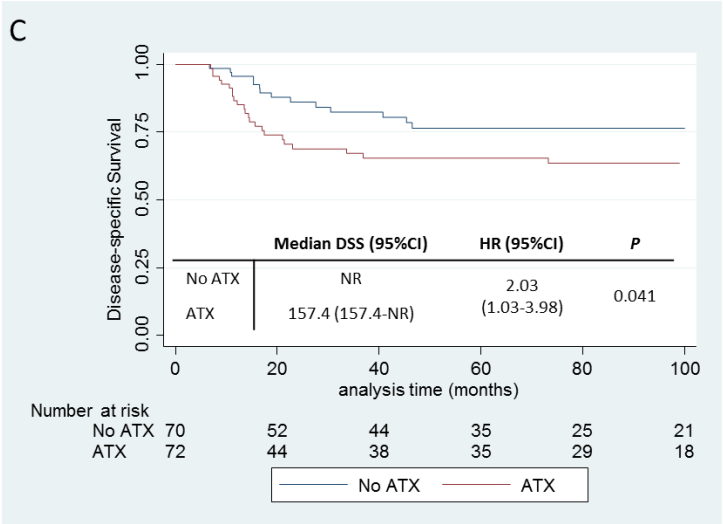
eFigure 1. Comparison between standard (panels A, C and E) and inverse probability of treatment-weighted Kaplan Meier curves (panels B, D and F).



eFigure 2. Kaplan Meier curves for overall survival (A), progression-free survival (B) and disease-specific survival (C) of patients with oropharyngeal carcinoma treated with induction chemotherapy.

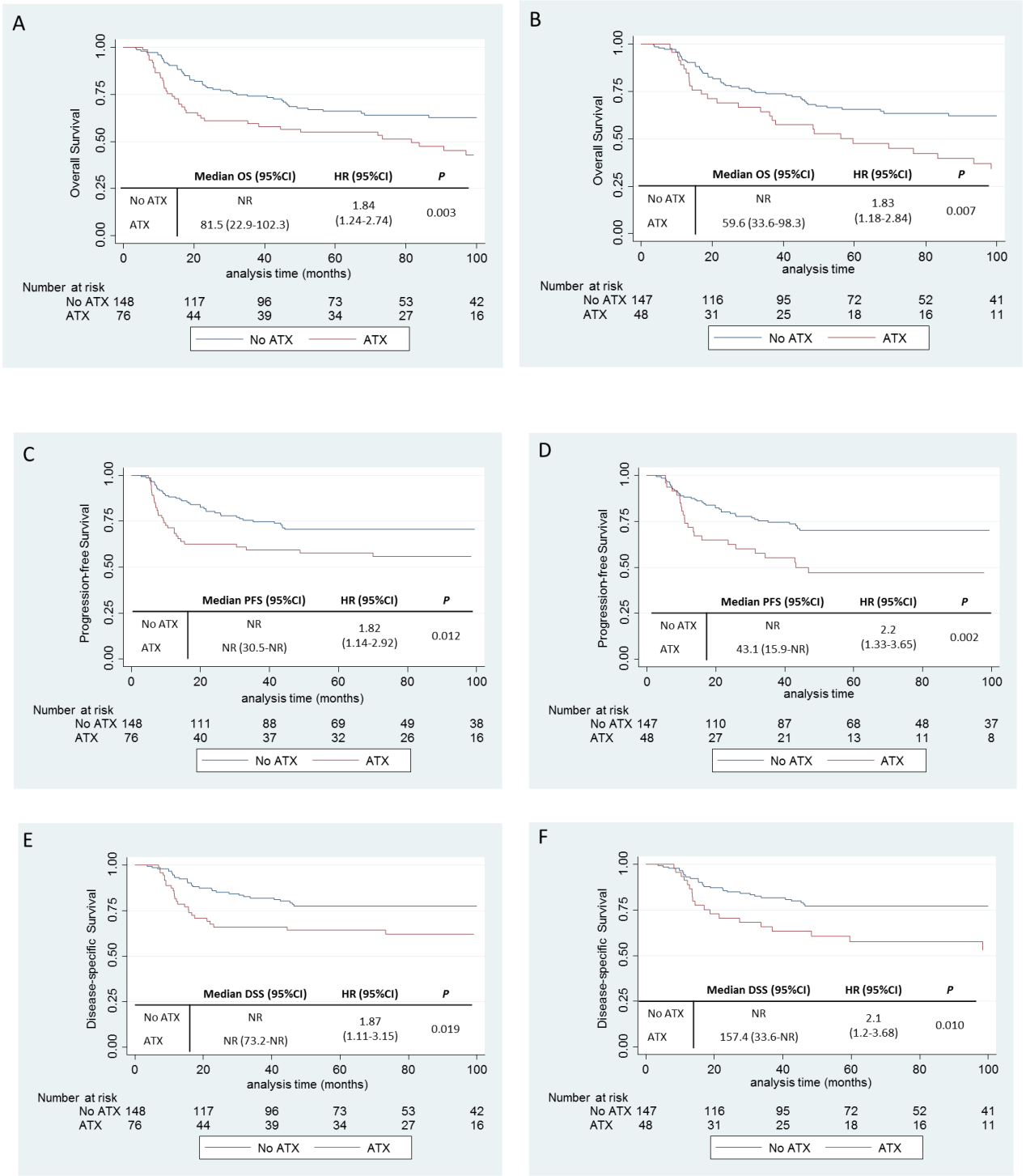




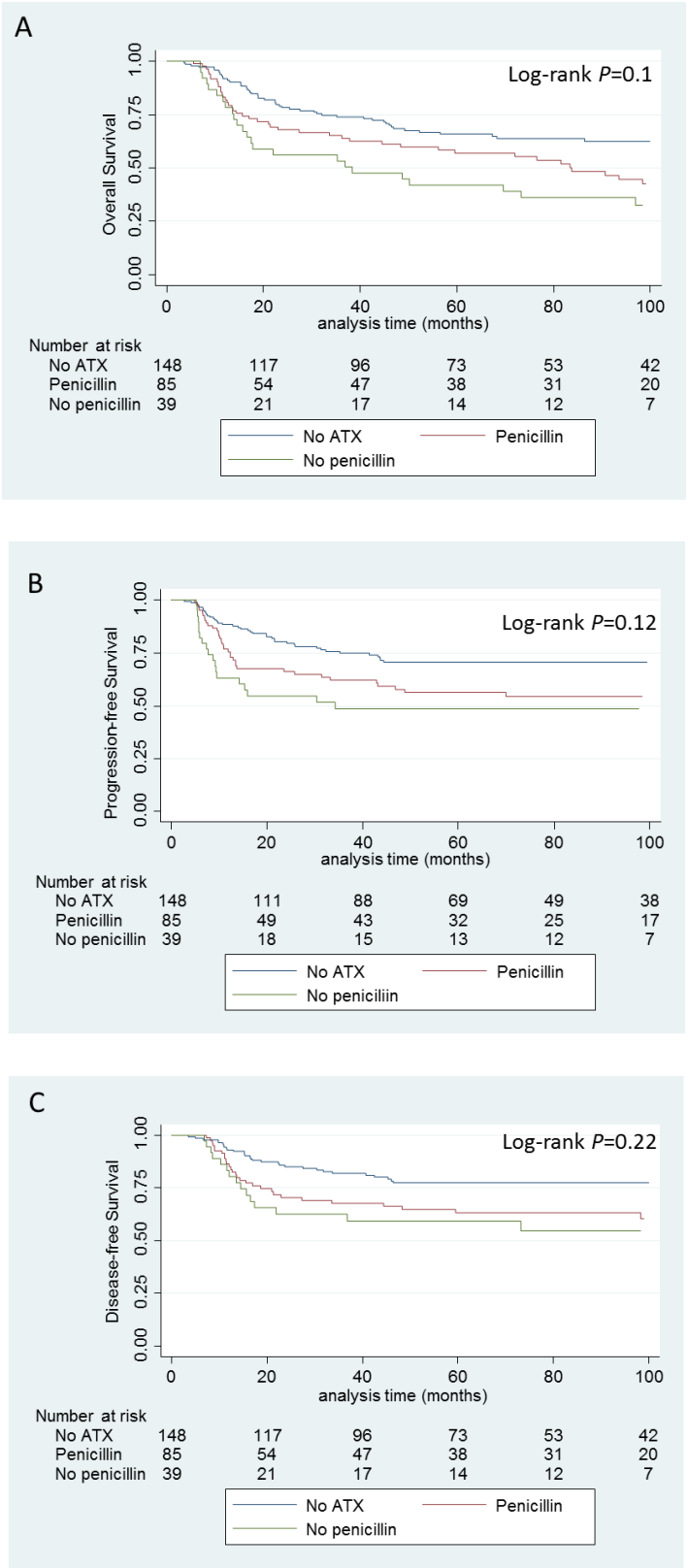


eFigure 3. Kaplan Meier curves for overall survival (panels A and B), progression-free survival (panels C and D) and disease-free survival (panels E to F) according to time prescribed during treatment (during induction vs. during RT).

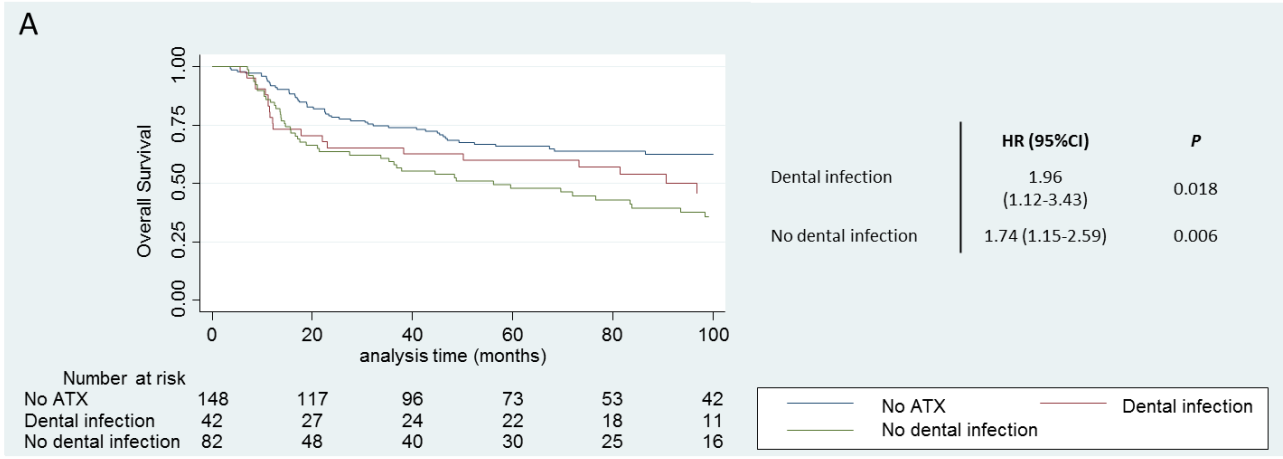
Antibiotic prescribed during IC | Antibiotic prescribed during RT

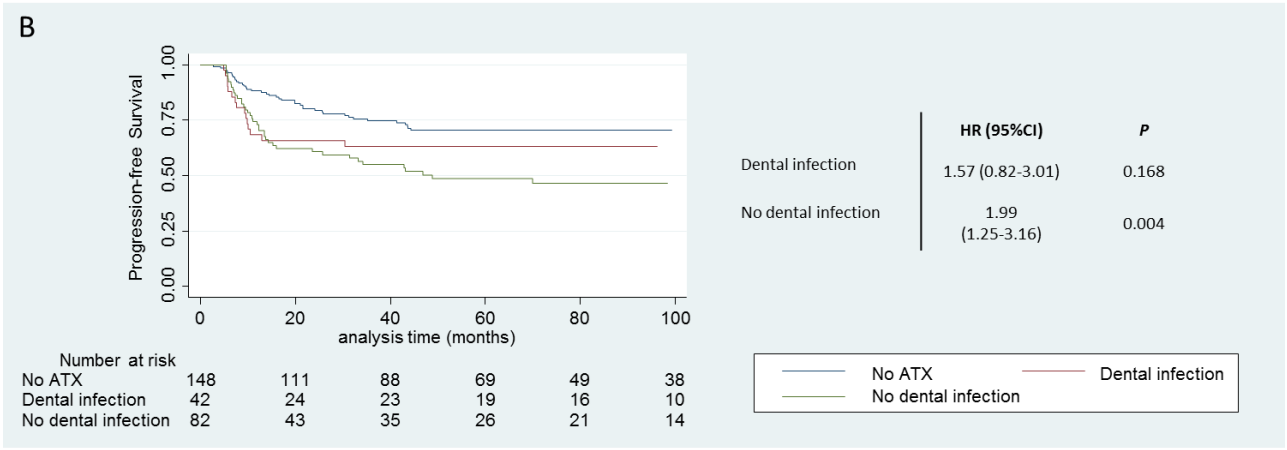


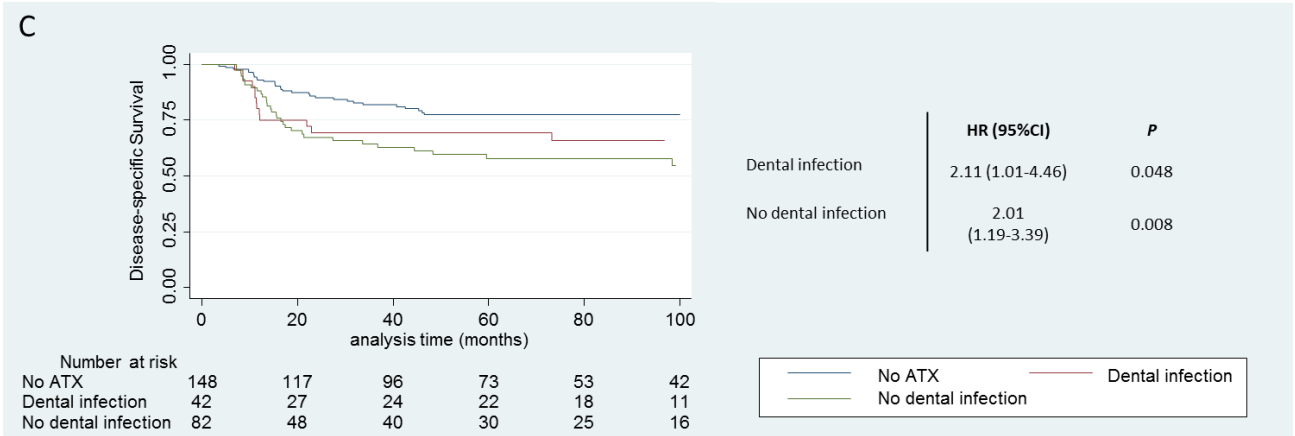
eFigure 4. Kaplan Meier curves for overall survival (A), progression-free survival (B) and disease-free survival (C) according to type of antibiotic (penicillin vs. no penicillin).



eFigure 5. Kaplan Meier curves for overall survival (A), progression-free survival (B) and disease-free survival (C) according to indication of prescription (dental infection vs. no dental infection).







eFigure 6. Kaplan Meier curves for loco-regional-recurrence-free survival (A) and distant metastases-free survival (B).