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Original Research

Nasopharyngeal cancer in non-endemic areas: Impact of treatment intensity within a large retrospective multicentre cohort

Paolo Bossi [a,b,*], Annalisa Trama [c], Alice Bernasconi [c], Salvatore Grisanti [a], Issa Mohamad [d], Isabel L. Galiana [e], Enis Ozyar [f], Pierfrancesco Franco [g], Stefania Vecchio [h], Pierluigi Bonomo [i], Beatriz C. Cirauqui [j], Mustafa El-Sherify [k], Stefano Ursino [l], Athanassios Argiris [m], Jonathan Pan [m], Claus Wittekindt [n], Elisa D'Angelo [o], Loredana Costa [p], Michela Buglione [p], Jennifer Johnson [m], Mario Airoldi [q], Ricard Mesia [j], Carlo Resteghini [b], Lisa Licitra [b,r], Ester Orlandi [s] On behalf of the Nasopharyngeal Cancer Portal Group of Investigators[1]

[a] *Medical Oncology Unit, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health-Medical Oncology, University of Brescia, ASST-Spedali Civili, Brescia, Italy*
[b] *Head and Neck Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale Dei Tumori, Via Venezian 1, Milan, 20133, Italy*
[c] *Evalutative Epidemiology Unit, Department of Research, Fondazione IRCCS Istituto Nazionale Dei Tumori, Via Venezian 1, Milan, 20133, Italy*
[d] *Department of Radiation Oncology, King Hussein Cancer Center, Amman, Jordan*
[e] *Radiation Oncology Department, Hospital Duran IReynals, Institut Català D'Oncologia-L'Hospitalet, Radiobiology and Cancer Group, IDIBELL, Barcelona, Spain*
[f] *Department of Radiation Oncology, Acibadem MAA University School of Medicine, Istanbul, Turkey*
[g] *Department of Translational Medicine (DIMET), University of Eastern Piedmont and AOU 'Maggiore Della Carita', Novara, Italy*
[h] *Medical Oncology, IRCCS San Martino, IST National Cancer Institute and University of Genova, Genova, Italy*
[i] *Radiation Oncology, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy*
[j] *Medical Oncology Department, Catalan Institute of Oncology - Badalona, B-ARGO Group, IGTP, Badalona, Spain*
[k] *Radiation Oncology Department, Kuwait Cancer Control Centre, Kuwait*

* *Corresponding author*: Piazzale Spedali Civili, 1, Brescia, 25123, Italy.
E-mail address: paolo.bossi@unibs.it (P. Bossi), annalisa.trama@istitutotumori.mi.it (A. Trama), alice.bernasconi@istitutotumori.mi.it (A. Bernasconi), grisanti.salvatore@gmail.com (S. Grisanti), imohamad@khcc.jo (I. Mohamad), ilinaresgaliana@iconcologia.net (I.L. Galiana), enis.ozyar@acibadem.com (E. Ozyar), pierfrancesco.franco@unito.it (P. Franco), stefania.vecchio@hsanmartino.it (S. Vecchio), bonomopierlu@gmail.com (P. Bonomo), bcirauqui@iconcologia.net (B.C. Cirauqui), mustafashawki@yahoo.com (M. El-Sherify), stefanoursino9@gmail.com (S. Ursino), athanassios.argiris@gmail.com (A. Argiris), jonathan.pan@jefferson.edu (J. Pan), Claus.Wittekindt@hno.med.uni-giessen.de (C. Wittekindt), dangelo.elisa@policlinico.mo.it (E. D'Angelo), lcosta77@libero.it (L. Costa), michela.buglione@unibs.it (M. Buglione), Jennifer.M.Johnson@jefferson.edu (J. Johnson), airoldim@yahoo.com (M. Airoldi), rmesia@iconcologia.net (R. Mesia), carlo.resteghini@istitutotumori.mi.it (C. Resteghini), lisa.licitra@istitutotumori.mi.it (L. Licitra), Ester.orlandi@cnao.it (E. Orlandi).
[1] Members of of the collaboration group listed in Appendix section.

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[l] Department of Radiation Oncology, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy
[m] Department of Medical Oncology, Thomas Jefferson University, Philadelphia, PA, United States
[n] Department of Otorhinolaryngology, Head and Neck Surgery, Medical Faculty, Justus-Liebig University Giessen, Giessen, Germany
[o] Radiation Oncology Unit, University Hospital of Modena, Italy
[p] Radiation Oncology Unit, Department of Medical and Surgical Specialties, Radiological Science and Public Health, ASST Spedali Civili of Brescia, University of Brescia, Brescia, Italy
[q] Medical Oncology, Città Della Salute e Della Scienza, Torino, Italy
[r] Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy
[s] Radiotherapy 2 Unit, Fondazione IRCCS Istituto Nazionale Dei Tumori, Milan, Italy

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KEYWORDS
Nasopharyngeal carcinoma (NPC); Epstein Barr-Encoded RNA (EBER); Intensity-modulated radiotherapy (IMRT); Induction chemotherapy (ICT); Adjuvant chemotherapy (ACT); Overall survival (OS); Disease-free survival (DFS)

Abstract ***Aim:*** Recommendations for managing patients with nasopharyngeal carcinoma (NPC) in non-endemic areas are largely derived from studies conducted in endemic areas. We analysed the impact of treatment approaches on survival in non-endemic areas.
Methods: In an international, multicentre, retrospective study, we analyse consecutive patients with NPC diagnosed between 2004 and 2017 in 36 hospitals from 11 countries. Treatment was categorised as non-intensive (NIT), including radiotherapy alone or concomitant chemoradiotherapy (cCRT), and intensive (IT) including cCRT preceded by and/or followed by chemotherapy (CT). The impact of IT on overall survival (OS) and disease-free survival (DFS) was adjusted for all the available potential confounders.
Results: Overall, 1021 and 1113 patients were eligible for overall survival (OS) and disease-free survival (DFS) analyses, respectively; 501 and 554 with Epstein Barr-encoded RNA (EBER) status available. In the whole group, 5-year OS was 84% and DFS 65%. The use of NIT was associated with a risk of death or recurrence 1.37 times higher than patients receiving IT. Patients submitted to NIT and induction CT + concurrent concomitant chemo and three-dimensional Conformal Radiation Therapy (3DCRT) had a risk of death or recurrence 1.5 and 1.7 times higher than patients treated with induction CT + cCRT with intensity-modulated radiotherapy (IMRT), respectively. The IT had no impact on OS in neither patients with EBER+ nor in patients with EBER-; IT showed better DFS in EBER+ but not in patients with EBER-.
Conclusions: In low-incidence areas, patients with NPC treated with induction CT followed by concurrent IMRT cCRT achieved the highest DFS rate. The benefit of IT on DFS was restricted to patients with EBER+, suggesting that additional therapy offers no advantages in EBER- cases.

1. Background

Nasopharyngeal carcinoma (NPC) has unique epidemiological and histological features. The global age-standardised incidence rates are high in Southern China and Southeast Asia (5–10 per 100,000), whereas they are much lower in most countries of the world, including Europe (1–2 per 100,000) [1,2]. In regions where NPC is endemic, most cases are non-keratinising subtypes invariably associated with Epstein–Barr virus (EBV) infection. In non-endemic areas, keratinising subtype is more common than in endemic regions, and the role of EBV is much less pronounced [3,4]. Epidemiological data about EBV-associated NPC are limited in non-endemic areas. An increase of EBV-related NPC subtype has been reported across genders and ethnicities in the United States leading to speculation of an increased role of EBV as a risk factor for NPC in this area [5]. However, the prevalence and prognostic significance of EBV-related NPC in non-endemic countries are not well-established because of the limited evidence [6,7].

The efficacy of different treatment strategies is mostly derived from prospective clinical trials and large retrospective series involving patients with NPC in endemic areas [8]. These data have been extrapolated to further guide treatment decisions in the non-endemic setting. In addition, whether treatment strategies defined in endemic areas can be also effectively applied in EBV negative NPC remains to be established.

We conducted a multicentre collaborative study to analyse the impact of clinical characteristics and treatment strategies on clinical outcomes of patients with NPC treated in non-endemic countries. In this study, we report on the effectiveness of intensive treatment (IT), the addition of induction or adjuvant chemotherapy (CT) to concomitant chemo-radiotherapy (cCRT), on NPC outcomes overall and by EBV status in non-endemic areas.

2. Materials and methods

We performed a multicentre retrospective observational study in non-endemic NPC areas (i.e. crude incidence rate ≤2/100,000 inhabitants) including centres in Europe (Belgium, Germany, Greece, Italy, the Netherlands, Spain, and Switzerland), Jordan, Kuwait, Turkey and the United States of America with experience in multidisciplinary management of patients with NPC (Fig. 1).

We included consecutive patients diagnosed with NPC (International Classification of Diseases for Oncology Third Edition topography codes for the site of origin C11 and histologic type keratinising squamous cell carcinoma 8071/3; non-keratinising carcinoma 8072/3 and basaloid squamous cell carcinoma 8083/3) between 2004 and 2016 and with a minimum follow-up of 12 months in 36 hospitals. Data entry started in January 2018 and closed in December 2018.

The following information were recorded: age; gender; Eastern Cooperative Oncology Group (ECOG) performance status; Epstein Barr-Encoded RNA (EBER) in tumour specimen (as determined by *in situ* hybridisation targeting the EBV-encoded small RNA − EBER − 1) and EBV-DNA plasma load before any treatment, data on primary tumour (e.g. clinical stage at diagnosis, treatment strategy etc.), treatment delivered, recurrence site and life status.

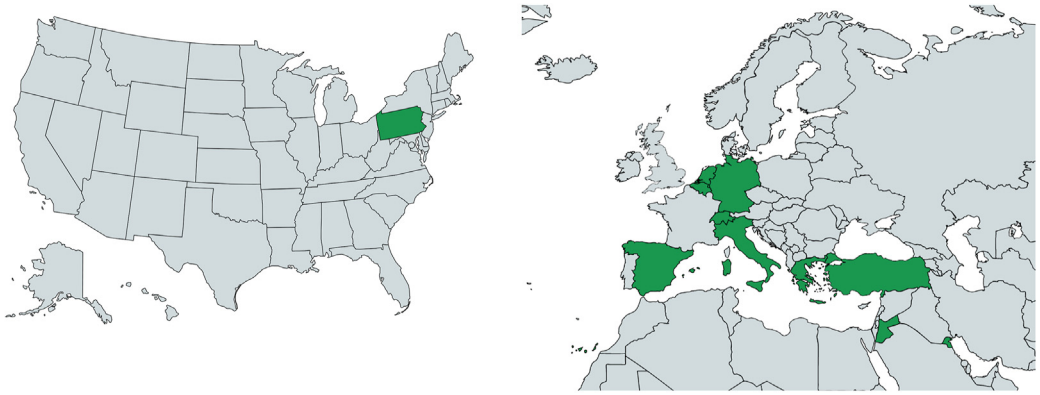
The stage was defined at cancer diagnosis as per the American Joint Committee on Cancer (AJCC) staging system 7th edition and combined in early (stage I-II) or advanced (stage III−IVa -IVb) or metastatic (stage IVc) to maximise the number of cases available for the survival analyses.

Age at diagnosis was categorised into≤65 years or >65 years [9]. Treatment approaches were further categorised as follows:

- Non-intensive (NIT), including
  - o Radiotherapy (RT) alone, either three-dimensional conformal radiation therapy (3DCRT) or intensity-modulated radiation therapy (IMRT) including static IMRT, volumetric modulated arc therapy and tomotherapy.
  - o cCRT, RT either 3DCRT or IMRT.
- IT (i.e. cCRT plus induction or adjuvant CT) which was further detailed in
  - o induction CT + cCRT (RT = 3DCRT);
  - o induction CT + cCRT (RT = IMRT);
  - o cCRT (RT = 3DCRT) + adjuvant CT;
  - o cCRT (RT = IMRT) + adjuvant CT;
  - o induction CT + cCRT (RT = IMRT) + adjuvant CT.
- Palliative approaches, consisting of CT alone or in combination with palliative RT.

Internal consistency verifications were performed to test data reliability on treatment, recurrence and life status.

We analysed patients' characteristics for the whole cohort and per EBER status. As information about EBER was limited, clinical prognostic characteristics (e.g. age, gender, histology, stage, treatment etc.) of patients with and without information about EBER were compared to confirm the absence of selection bias for the group with EBER information. Comparison between EBER+ and EBER- patients' characteristics were done using T-test (for continous variables) and Chi-squared test (for categorical variables): only p-values are reported.



Country	USA	Turkey	Italy	Germany	Spain	Greece	Jordan	The Netherlands	Belgium	Switzerland	Kuwait
Crude rate	0.65	1.1	0.99	0.52	0.81	1.5	0.81	0.46	0.63	0.61	0.69

Fig. 1. Geographical areas contributing to the study together with the nasopharyngeal cancer crude incidence rate observed in the area.

Table 1
Clinical characteristics and treatment strategies of patients included in the study overall and by EBER status.

	Overall N = 1230	EBER + N = 511	EBER- N = 114	Comparison EBER+ and EBER-
Age, years				p-value = 0.5064
mean (SD)	49.9 (14.8)	48.8 (15.0)	49.9 (15.4)	
Age (%)				p-value = 0.787
<65 (%)	1012 (82%)	425 (83%)	96 (84%)	
≥65 (%)	218 (18%)	86 (17%)	18 (16%)	
Sex (%)				p-value = 0.105
Male	885 (72%)	375 (73%)	75 (66%)	
Female	345 (28%)	136 (27%)	39 (34%)	
Histology (%)				p-value<0.001
Keratinising	146 (12%)	38 (7%)	25 (22%)	
Non-keratinising	1051 (86%)	464 (91%)	80 (70%)	
Basaloid	18 (1%)	6 (1%)	8 (7%)	
Missing	15 (1%)	3 (1%)	1 (1%)	
Stage at diagnosis (%) (AJCC 7th edition)				p-value = 0.080
Stage I-II	246 (20%)	83 (16%)	23 (20%)	
Stage III-IVa-IVb	875 (71%)	372 (73%)	82 (72%)	
Stage IVc	58 (5%)	42 (8%)	3 (3%)	
Missing	51 (4%)	14 (3%)	6 (5%)	
Treatment (%)				p-value = 0.020
RT alone	87 (7%)	24 (5%)	11 (10%)	
- IMRT	60 (69%)	15 (63%)	10 (91%)	
- 3DCRT	27 (31%)	9 (37%)	1 (9%)	
cCRT alone	448 (37%)	159 (31%)	46 (40%)	
- CT and IMRT	336 (75%)	142 (89%)	29 (63%)	
- CT and 3DCRT	98 (22%)	12 (8%)	17 (37%)	
- CT and radio type missing	14 (3%)	5 (3%)	0 (0%)	
Intensive treatment	664 (54%)	310 (61%)	55 (48%)	
- Induction CT + cCRT (RT = 3DCRT)	72 (11%)	17 (6%)	3 (5%)	
- Induction CT + cCRT (RT = IMRT)	440 (66%)	229 (74%)	34 (62%)	
- cCRT (RT = 3DCRT) +adjuvant CT	83 (13%)	26 (8%)	13 (24%)	
-cCRT (RT = IMRT) + adjuvant CT	32 (5%)	11 (4%)	2 (4%)	
-Induction CT + cCRT (RT = IMRT) + adjuvant CT	35 (5%)	26 (8%)	3 (5%)	
-Intensive treatment details missing	2 (0%)	1 (0%)	0 (0%)	
Palliative	28 (2%)	18 (3%)	2 (2%)	
Missing	3 (0%)	0 (0%)	0 (0%)	

3DCRT, three-dimensional conformal radiation therapy; CT, chemotherapy; AJCC, American Joint Commission on Cancer; cCRT, concomitant chemoradiotherapy; EBER+, Epstein Barr-encoded virus+; IMRT, intensity-modulated radiotherapy; RT, radiotherapy; SD, standard deviation.

2.1. Ethics committee approval

Ethics approval was obtained from all concerned Institutional Review Boards and the Ethics Committees.

2.2. Survival analysis

Overall survival (OS) was defined as the time between the date of treatment end and the date of last follow-up/contact or death. We excluded the time between cancer diagnosis and treatment completion to account for potential immortal time bias [10]. Disease-free survival (DFS) was defined as the time between the date of treatment completion and the date of first recurrence, last follow-up/contact or death. Both OS and DFS were cut at 5 years and analysed using the Kaplan–Meier survival method; survival curves were compared using the log-rank test. Five-year OS and DFS were estimated for the whole cohort and per EBER status.

Patients were excluded from OS and DFS analysis if they had any of the following: basaloid squamous cell carcinoma; metastasis at diagnosis and/or received only palliative care; unreliable dates (Supplementary Fig. 1, Appendix A).

We fitted Cox proportional hazard models for the whole cohort and for EBER-specific analyses [11]. The maximum likelihood bottom-up approach was used to identify the prognostic variables to be considered in the models [12]. This approach starts from a simple model and adds variables one at a time till the null model is not rejected. Our objective was to estimate the impact of IT on OS and DFS, adjusted for all the possible confounders. Thus, we ran a model including only treatment variables and subsequently added variables with significant influence on treatment effect on OS and DFS. Variables tested included gender, histological type, clinical stage, ECOG performance status, age at diagnosis, EBER status and time period of diagnosis defined as 2004–2009 versus 2010–2016.

Table 2
Treatment strategies by stage overall and by EBER status.

	Overall					EBER+					EBER-				
Treatment	N°	Stage I-II (%)	Stage III-IVa-b (%)	Stage IVc (%)	Stage Missing (%)	N°	Stage I-II(%)	Stage III-IVa-b (%)	Stage IVc(%)	Stage Missing (%)	N°	Stage I-II (%)	Stage III-IVa-b (%)	Stage IVc (%)	Stage Missing (%)
RT only	88	51 (21%)	29 (3%)	2 (4%)	6 (12%)	24	12 (14%)	10 (3%)	1 (2%)	1 (7%)	11	7 (30%)	3 (4%)	1 (33%)	0 (0%)
cCRT only	448	135 (55%)	298 (34%)	2 (4%)	13 (25%)	159	49 (59%)	102 (27%)	2 (5%)	6 (43%)	46	11 (48%)	34 (41%)	0	1 (17%)
Intensive treatment	664	60 (24%)	543 (62%)	30 (51%)	31 (61%)	310	22 (27%)	260 (70%)	21 (50%)	7 (50%)	55	5 (22%)	45 (55%)	1 (33%)	4 (67%)
Palliative	30	0 (0%)	5 (1%)	24 (41%)	1 (2%)	18	0 (0%)	0 (0%)	18 (43%)	0 (0%)	2	0 (0%)	0 (0%)	1 (33%)	1 (17%)
Total	1230	246	875	58	51	511	83	372	42	14	114	23	82	3	6

cCRT, concomitant chemoradiotherapy; EBER, Epstein Barr-encoded virus+; RT, radiotherapy.

We used multiple imputations to minimise missing data in the variables tested, after checking that data were missing completely at random [13]. We tested the collinearity between variables included in the models by the variance inflation factor [14]. Survival statistics were computed using Stata 13 software.

3. Results

3.1. Clinical and treatment characteristics

Overall, 1230 cases were registered. After patient's exclusion owing to the aforementioned criteria, 1021 patients were considered for OS and 1113 patients for DFS analysis. Clinical characteristics and treatment strategies are reported in Table 1 for all 1,230 registered cases.

The mean age was 50 years, and most patients were men and with advanced stage at diagnosis.

The male:female ratio was 2.8, 2.6 and 1.9 for the whole cohort, EBER+ and EBER- cases, respectively. Most patients with NPC had non-keratinising histology, which was more common in EBER+ versus EBER- cases (91% vs 70%, $p < 0.001$).

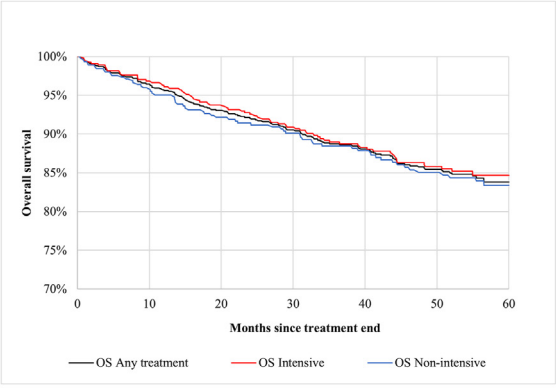
Analysis by EBER status included 501 patients for the OS (417 EBER+ and 84 EBER-) and 554 patients for DFS analyses (455 EBER+ and 99 EBER-) (Supplementary Fig. 1, Appendix A), whereas EBV DNA was performed only in 274 of 1230 cases, therefore preventing any analysis with this factor.

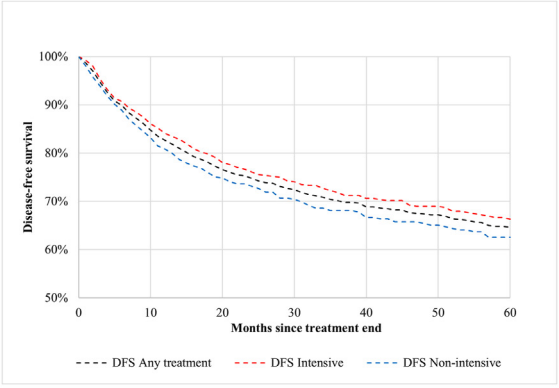
The group of patients with no EBER information did not show any significant clinical difference compared with the group with EBER information (Supplementary Tabs. 1–2, Appendix A).

To evaluate the presence of distant metastasis, 55% of patients received Fluorodeoxyglucose-positron-emission tomography (PET). The remaining patients received a conventional work-up including thorax computed tomography scan, abdominal computed tomography scan or ultrasonography and skeletal scintigraphy. Staging with PET scan increased during time, with 41% of patients having received PET in the 2004–2009 period and 62% between 2010 and 2016 (data not in Tables).

Overall, ITs were adopted in about half of NPC cases, more frequently in patients with EBER+. IMRT was the most used radiotherapy technique in all subgroups, alone, with concurrent chemotherapy and within IT approaches. The most common IT approach consisted of induction CT followed by cCRT with IMRT. Among patients treated with induction CT, 61% received a three-drug combination and 36% a two-drug scheme. Three cycles were administered to 60% of the patients, whereas two cycles to 38%. Considering adjuvant CT, most of the patients received a combination with platinum and 5-fluorouracil (81%), and more than two cycles were administered to 59% of the patients.

Table 2 shows that 24% of patients with early disease at diagnosis (stage I-II) were treated with IT, whereas





Log-rank test (intensive vs non-intensive)	
Chi-squared	P-value
0.16	0.6877

Months since treatment end		0-12	12-24	24-36	36-48	48-60
Any treatment	Patients at risk	1021	908	820	707	579
	Events	42	34	28	22	9
	Censored	71	54	85	106	570
Intensive	Patients at risk	553	503	455	398	328
	Events	20	19	17	11	5
	Censored	30	29	40	59	323
Non intensive	Patients at risk	468	405	365	309	251
	Events	22	15	11	11	4
	Censored	41	25	45	47	247

Log-rank test (intensive vs non-intensive)	
Chi-squared	P-value
1.97	0.1600

Months since treatment end		0-12	12-24	24-36	36-48	48-60
Any treatment	Patients at risk	1113	862	717	600	489
	Events	176	82	45	23	19
	Censored	75	63	72	88	470
Intensive	Patients at risk	610	485	409	350	290
	Events	87	47	23	15	10
	Censored	38	29	36	45	280
Non intensive	Patients at risk	503	377	308	250	199
	Events	89	35	22	8	9
	Censored	37	34	36	43	190

Fig. 2. Overall and disease-free survival by type of treatment.

76% were treated with NIT (either RT or cCRT alone). Most of early-stage patients treated with IT were <65 years old. Thirty-seven per cent of patients with advanced stage at diagnosis were treated with NIT and 62% with IT. Young patients (i.e. < 65 years old) were more likely to be treated with IT. Patients with advanced disease were more frequently treated with IT if EBER+ (70% of the advanced cases). However, 55% of advanced disease, patients with EBER- received IT (Table 2).

3.2. Outcome results

Five-year OS for the whole cohort was 84% (92% for stage I-II and 81% for stage III-IV; $p < 0.001$, Supplementary Fig. 2, Appendix A) and did not differ by type of treatment (Fig. 2). However, 5-year DFS was 65% (79% for stage I-II and 61% for stage III-IV; $p < 0.001$, Supplementary Fig. 3, Appendix A), and it was higher in patients with NPC treated with IT (66%) compared with those treated with NIT (63%), Fig. 2.

OS and DFS as per stage and EBER status are reported in Supplementary Figs. 4–7, Appendix A.

OS in patients with EBER+ and EBER- did not differ by type of treatment (NIT vs IT). DFS in patients with EBER+ was higher in IT-treated cases, whereas in patients with EBER- treatment intensity had no significant impact (Figs. 3 and 4).

Cox proportional hazard models assessing IT impact on OS and DFS in the whole cohort of patients with NPC are shown in Table 3. IT was distinguished in 'induction + cCRT' and 'cCRT + adjuvant' to analyse their prognostic role. These different IT approaches had no independent impact on OS.

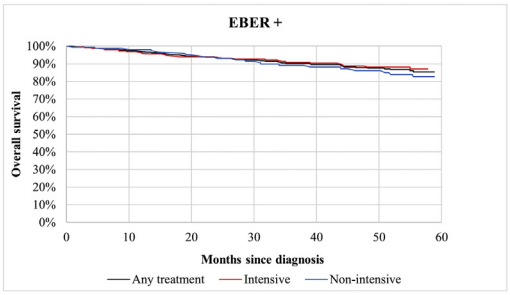
Compared with patients treated with induction CT + cCRT (RT = IMRT), the risk of death or recurrence was 1.7 times ($p = 0.01$) higher for patients treated with induction CT + cCRT (RT = 3DCRT) and 1.5 times higher ($p = 0.01$) for patients treated with a NIT approach. Patients with NPC treated with IT treatment (IMRT or 3DCRT) + adjuvant CT had an excess risk of death or recurrence (hazard ratio [HR]> 1), although this result was not statistically significant.

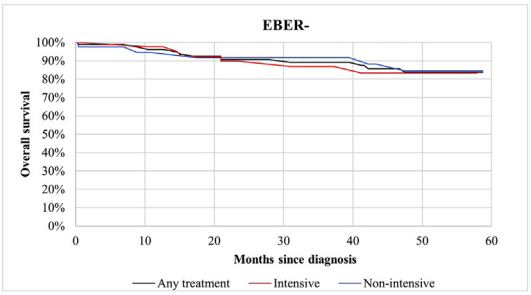
Table 4 reports the same analyses as per EBER status. The model confirmed that, at the net of confounding factors, IT did not impact OS in neither patients with EBER+ nor in patients with EBER-. Advanced stage, age (>65 years old) and years of diagnosis 2004–2009 were significant prognostic factors for patients with EBER+.

However, IT showed a positive impact on DFS in EBER+ cases where the risk of recurrence was almost 2 times higher (HR = 1.8; $p < 0.001$) for NIT versus IT treated patients. Advanced stage and male gender were other prognostic factors for patients with EBER+. Age> 65 years old was the only significant prognostic factor for patients with EBER-.

4. Discussion

To our knowledge, the current study represents the largest series of patients with NPC collected in non-endemic areas. It focuses on the use and impact of IT, defined as any addition of CT to cCRT (either in the





Log-rank test (intensive vs non-intensive)	
Chi-squared	P-value
0.74	0.3898

Log-rank test (intensive vs non-intensive)	
Chi-squared	P-value
0.04	0.8350

Months since treatment end		0-12	12-24	24-36	36-48	48-60
Any treatment	Patients at risk	417	379	347	298	239
	Events	12	13	12	7	5
	Censored	26	19	37	52	234
Intensive	Patients at risk	257	236	220	194	158
	Events	9	7	6	4	2
	Censored	12	9	20	32	156
Non intensive	Patients at risk	160	143	127	104	81
	Events	3	6	6	3	3
	Censored	14	10	17	20	78

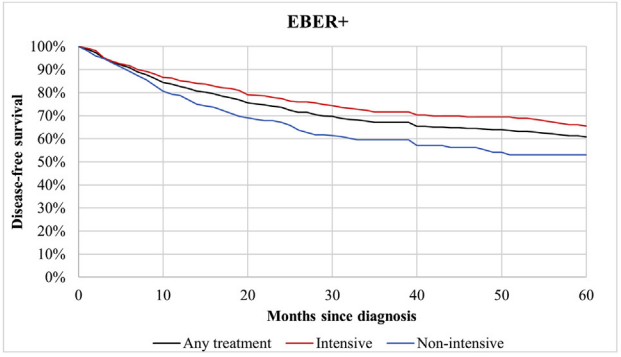
Months since treatment end		0-12	12-24	24-36	36-48	48-60
Any treatment	Patients at risk	84	72	61	56	40
	Events	4	4	1	3	0
	Censored	8	7	4	13	40
Intensive	Patients at risk	43	40	30	27	18
	Events	1	3	1	1	0
	Censored	2	7	2	8	18
Non intensive	Patients at risk	41	32	31	30	22
	Events	2	1	0	2	0
	Censored	7	0	1	6	22

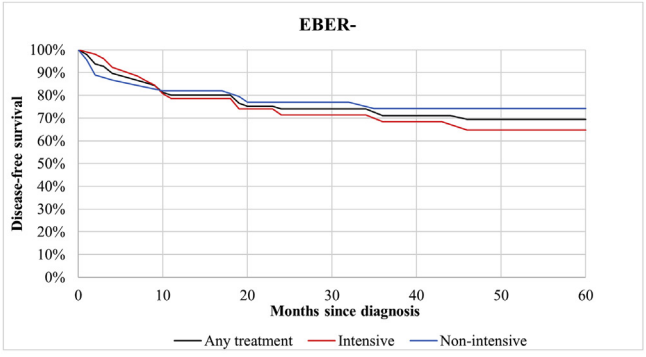
Fig. 3. Overall survival by type of treatment and by EBER status. EBER, Epstein Barr-encoded RNA.

induction and/or adjuvant setting). We observed that IT was employed twice as much as chemoradiation alone in locally advanced stages. Moreover, it has been more frequently used in patients with EBER+ (70% of cases) compared with EBER- cases in which nearly half of patients (55%) received IT. Interestingly, patients with EBER- were more likely to receive adjuvant CT compared with EBER+ cases. This may reflect the influence on oncologists of the well-known intergroup trial results, which used cCRT followed by adjuvant CT in non-endemic countries [15].

Our study showed the prevalence of 82% of EBV in our multicentric unselected population. Of course, this needs to be validated on a nationwide scale.

In areas where the disease is endemic, treatment intensification has shown to produce increased survival rates, even if the process for best patient's selection for this approach has not been fully elucidated [16,17]. The application of IT in non-endemic areas is a matter of debate, and real-world data, like ours, could contribute to increase knowledge and better discuss this strategy feasibility and utility.





Log-rank test (intensive vs non-intensive)	
Chi-squared	P-value
7.66	0.0057

Log-rank test (intensive vs non-intensive)	
Chi-squared	P-value
0.40	0.5271

Months since treatment end		0-12	12-24	24-36	36-48	48-60
Any treatment	Patients at risk	455	358	303	252	201
	Events	72	40	28	9	10
	Censored	25	15	23	42	191
Intensive	Patients at risk	282	232	201	171	145
	Events	38	22	16	5	7
	Censored	12	9	14	21	138
Non intensive	Patients at risk	173	126	102	78	56
	Events	34	18	12	4	3
	Censored	13	6	12	18	53

Months since treatment end		0-12	12-24	24-36	36-48	48-60
Any treatment	Patients at risk	99	73	57	51	40
	Events	19	4	2	2	0
	Censored	7	12	4	9	40
Intensive	Patients at risk	53	39	28	24	17
	Events	11	2	1	2	0
	Censored	3	9	3	5	17
Non intensive	Patients at risk	46	34	29	27	23
	Events	8	2	1	0	0
	Censored	4	3	1	4	23

Fig. 4. Disease-free survival by type of treatment and by EBER status. EBER, Epstein Barr-encoded RNA.

Table 3
Impact on overall survival (3a) and disease-free survival (3b) of the intensive treatment and of type of intensive treatment (Induction + cCRT (RT = 3D); Induction + cCRT (RT = IMRT); cCRT (RT = IMRT) + adjuvant; cCRT (RT = 3D) + adjuvant) 3c and 3d.

Overall survival				
3a				
Variable	HR	p-value	95% confidence	interval
Intensive	ref			
Non-intensive	1.12	0.55	0.78	1.60
Stage I–II	ref			
Stage III–IV	3.34	<0.001	1.91	5.85
Age<=65	ref			
Age>65	3.75	<0.001	2.58	5.45
2010–2017	ref			
2004–2009	1.99	<0.001	1.41	2.81
3c				
Variable	HR	p-value	95% confidence	interval
Non-intensive	1.26	0.27	0.84	1.89
Induction + cCRT (RT=3DCRT)	1.62	0.14	0.86	3.05
Induction + cCRT (RT = IMRT)	ref			
cCRT (RT = IMRT) + adjuvant	1.92	0.09	0.90	4.13
cCRT (RT = 3DCRT) +adjuvant	0.84	0.74	0.30	2.37
Stage I–II	ref			
Stage III–IV	3.39	<0.001	1.94	5.93
Age<=65	ref			
Age>65	3.76	<0.001	2.57	5.49
2010–2017	ref			
2004–2009	2.01	<0.001	1.39	2.89
Disease-free survival				
3b				
Variable	HR	p-value	95% confidence	interval
Intensive	ref			
Non-intensive	1.37	0.01	1.10	1.71
Stage I–II	ref			
Stage III–IV	2.64	<0.001	1.90	3.66
Age<=65	ref			
Age>65	1.61	<0.001	1.24	2.09
Female	ref			
Male	1.55	<0.001	1.20	2.01
3d				
Variable	HR	p-value	95% confidence	interval
Non-intensive	1.49	0.01	1.16	1.91
Induction + cCRT (RT = 3DCRT)	1.7	0.01	1.12	2.57
Induction + cCRT (RT = IMRT)	ref			
cCRT (RT = IMRT) + adjuvant	1.19	0.49	0.73	1.93
cCRT (RT = 3DCRT) +adjuvant	1.11	0.75	0.58	2.12
Stage I–II	ref			
Stage III–IV	2.65	<0.001	1.91	3.68
Age<=65	ref			
Age>65	1.55	<0.001	1.19	2.03
Female	ref			
Male	1.53	<0.001	1.18	1.98

3DCRT, three-dimensional conformal radiation therapy; cCTRT, concomitant chemoradiotherapy; HR, hazard ratio; IMRT, intensity-modulated radiotherapy; RT, radiotherapy.

In this regard, the present study supports the use of IT approaches to improve DFS in locally advanced NPC. The use of NIT was associated with a 37% higher risk of relapse or death. This reflects what has been shown in a meta-analysis of studies performed in endemic areas, where induction CT plus cCRT was superior to cCRT [18]. However, in our analyses, IT did not show a clear advantage in terms of OS. The benefit of IT for DFS but not for OS could have different explanations: primarily, the increased use of salvage local therapy for limited locoregional recurrences such as surgery or conformational techniques of RT; second, the availability of several active systemic therapies in case of distant recurrences [19,20].

Table 4
Impact of the intensive treatment on overall survival and disease-free survival by EBER status.

Overall survival				
EBER+				
Variable	HR	p-value	95% confidence	interval
Intensive	ref			
Non-intensive	1.45	0.22	0.80	2.64
Stage I-II	ref			
Stage III-IV	3.06	0.02	1.16	8.04
Age<=65	ref			
Age>65	2.6	0.01	1.30	5.20
2010–2017	ref			
2004–2009	1.89	0.03	1.07	3.36
EBER-				
Variable	HR	p-value	95% confidence	interval
Intensive	ref			
Non-intensive	0.88	0.84	0.27	2.90
Disease-free survival				
EBER+				
Variable	HR	p-value	95% conf	interval
Intensive	ref			
Non-intensive	1.80	<0.001	1.30	2.50
Stage I-II	ref			
Stage III-IV	2.03	<0.001	1.27	3.24
Female	ref			
Male	1.72	0.01	1.16	2.56
EBER-				
Variable	HR	p-value	95% conf	interval
Intensive	ref			
Non-intensive	0.67	0.32	0.31	1.47
Age<=65 years	ref			
Age >65 years	3.31	0.01	1.37	8.04

EBER, Epstein Barr-encoded virus, HR, hazard ratio.

Interestingly, in the subgroup of patients with known tumoral EBER status, the benefit of IT on DFS was restricted to patients with EBER+. This might reflect a higher chemosensitivity of EBV-related cases, which is mirrored by the physicians' attitude towards administering more systemic treatments in this disease subgroup. EBV-related NPC has a high metastasizing capacity owing to the peculiar genomic alterations induced by EBV, which promotes distant dissemination by Nuclear factor-kappaB signalling pathway [21,22]. Therefore, it is conceivable that a higher number of chemotherapy cycles could have an impact on DFS mainly for EBER+ cases, reducing the risk of distant spread.

In addition, the study results show that patients with EBER- would not benefit from an IT approach, suggesting that they should be managed as typical head and neck squamous cell carcinomas in sites other than the nasopharynx, where cCRT alone is the standard of care. Furthermore, the keratinising histology is associated with a lower rate of distant metastasis compared with non-keratinising carcinoma, which is invariably associated with EBV, remarking the most common use of IT in the latter histology [23,24]. Considering these data and the challenges of designing a randomised trial in a low incidence scenario, one could advocate for the use of cCRT in locally advanced EBER-NPC, because additional therapy seems to offer no advantages.

We showed that among IT approaches, induction CT followed by cCRT with IMRT achieved the highest rate of DFS. IMRT is an important milestone in the management of NPC, providing minimal late effects and non-inferior outcomes compared with prior RT techniques [25]. Our results are partially aligned with a network meta-analysis performed on 27 trials and 7,940 patients, which showed that in the IMRT era, for OS, PFS and distant metastasis-free survival, induction CT followed by cCRT was the most effective regimen when compared with cCRT followed by adjuvant CT and cCRT alone [18]. This has been recently confirmed by the results of an individual patient data network meta-analysis. The authors showed that induction chemotherapy with taxanes followed by cCRT ranked as the best treatment in terms of OS more than cCRT alone or with adjuvant CT [26].

Among the other variables considered in our model, we may highlight the role of the treatment era in

determining a better OS rate. Several factors have probably played a role, including diagnostic advances, stage migration owing to improved disease assessment by radiological imaging, better patient's selection, RT technique optimisation, improvement in supportive care to mitigate toxicities and optimisation of salvage therapy for recurrent or metastatic disease.

We acknowledge the limitations of our analysis, mainly consisting of its retrospective nature, and the voluntary collection of data, limited number of EBER status information which limited the analysis, the known doctors' decision-making bias and the lack of an updated staging. In addition, we are aware of the existence of biases in selecting treatment approaches, who were left to the choice of the multidisciplinary group of each centre. Therefore, when different treatment options were available as per guidelines, the decision process to adopt IT or NIT strategy cannot be retrospectively defined. Moreover, no data about acute toxicities are available owing to the retrospective nature of the analysis.

However, this series represents the largest available clinical data collection defining the outcome of non-endemic patients with NPC. In the context of rare cancers, the use of retrospective data derived from registries or multicentre data collection represents an opportunity to support the clinical management and drive the therapeutic approaches [27,28]. In this regard, the current analysis does not suggest new approaches to NPC, but it supports the transposability of IT in non-endemic patients with EBER+ NPC, and it confirms the peculiar clinical behaviour of EBER- cases.

In the future, the collection of prospective data coming from institutions of non-endemic areas will help in further refining the choice of treatment approach, together with other factors influencing prognosis such as circulating EBV DNA and pre-treatment patient's quality of life, which has been associated with survival in endemic areas [29].

Authors' contributions

All the authors: Data curation, validation, writing-original draft and writing-review and editing. Trama and Bernasconi: in addition, formal analysis, investigation, software and methodology. Bossi and Orlandi: also, conceptualisation, project administration and methodology.

Role of the funding source

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Conflict of interest statement

Bossi reports personal fees from Merck, Sanofi Regeneron, BMS, MSD, GSK, Astrazeneca, Sunpharma, Angelini and grants from GSK and Sunpharma, outside the submitted work. Buglione reports personal fees from Meck Serono, outside the submitted work. Cirauqui Cirauqui reports congress support from MSD, Merck, BMS and Roche, and personal fees from BMS and Roche, outside the submitted work. Ursino reports grants from Merck Serono, Nestlé, Kyowakirin and Astra Zeneca, outside the submitted work. D'angelo reports personal fees from Astra Zeneca, Nestlé and Merck Spa, outside the submitted work. Licitra reports personal fees and grants from Astra Zeneca, Bayer, BMS, Boehringer ingelheim, Debiopharm International SA, EISAI, Merck Serono MSD, Novartis, Roche; Personal fee from Bayer, SOBI, IPSEN, GSK, Doxa Pharma srl, Incyte Biosciences Italy srl, Amgen, Nanobiotics Sa; Grants from Celgene International, Exelixis inc, grants Hoffmann-La Roche ltd, IRX Therapeutics inc Medpace inc, grants Pfizer, outside the submitted work. Mesia reports Consulting and advisory role for Merck, MSD, Roche, Asta Zeneca, BMS and speaker's Bureau for Merck, MSD, BMS, Roche. All the other authors have nothing to disclose.

Appendix - Other components of the Nasopharyngeal Cancer Portal Group of Investigators

Martín Martín, Paolo Battaglia, Mario Turri-Zanoni, Marco Lionello,Giuseppe Azzarello, Giorgia Boscolo, Cecilia Moro, Laura Maffioletti, Eva Iannacone, Isabella Garassino, Robert J. Baatenburg de Jong, Josè Hardillo, Cataldo Mastromauro, Sara Menazza,Simona Secondino, Biella Francesco Montagnani, Fable Zustovich, Donatella Da Corte, Filippo De Renzi, Giuseppe Aprile, Francesca Pancheri, Ciro Rossetto, Massimo Ghiani, Paolo Carta, Alessandra Dessì, Maria Chiara Cau, Salinas Ramos, Harilena Charoula, Eleni Giannakopoulou, HildeVerstraete, Daan Nevens, Montse Velasco, Teresa Bonfill, Encarna Mur Restoy, Alessandra Franzetti-Pellanda

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.09.005.

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