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Phase III Randomized Study of Induction Chemotherapy Followed by Definitive Radiotherapy + Cetuximab Versus Chemoradiotherapy in Squamous Cell Carcinoma of Head and Neck: The INTERCEPTOR-GONO Study (NCT00999700)

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Keywords
Cetuximab · LASCCHN · Induction chemotherapy · Chemoradiotherapy

Abstract
Objectives: Induction chemotherapy followed by cetuximab and RT (IBRT) (Arm A) was compared to cisplatin/RT (CRT) (Arm B) in a randomized phase III study. ***Patients and Methods:*** Naïve patients with stage III-IVa, histologically proven locally advanced head and neck cancer (LASCCHN) were eligible. Arm A (IBRT): 3 TPF induction followed by cetuximab-RT (equivalent daily dose 2 Gy up to 70 Gy); Arm B: 3 cisplatin concurrent with the same RT scheduling. Due to slow accrual and incomplete data collection a futility analysis was performed. ***Results:*** 236/282 patients were evaluable. Therefore, no formal analyses can be made between the two arms. OS was 45.2/53.6 months in Arm A/B. Complete responses were achieved in 64% of patients in both arms. Neutropenia and skin toxicity were significantly worse in Arm A and body weight loss was significantly worse in Arm B. Compliance with the planned drug administration was higher in Arm B ($p = 0.0008$). ***Conclusion:*** The study suggests that IBRT and CRT have similar efficacy, activity and toxicity.

Introduction

Locally advanced head and neck cancer (LASCCHN) remains a major challenge among the human solid tumors with a limited proportion of long-term survivors notwithstanding the use of aggressive combined therapies [1].

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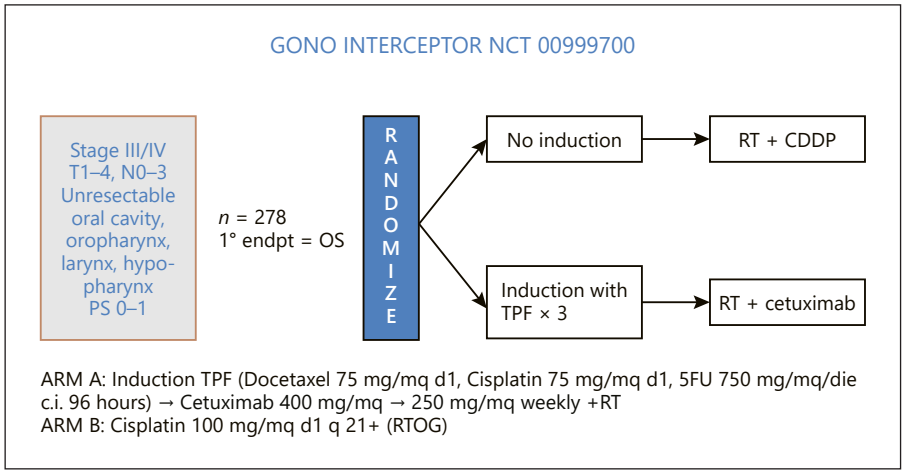


Fig. 1. Study design.

Platinum-based chemotherapy concurrent with radiotherapy (CRT) compared to radiotherapy alone was shown to produce an 8% increase in 5-year survival benefit in a large meta-analysis [2]. The benefit was later confirmed by an update of the same meta-analysis, which included new studies [3]. Induction chemotherapy (IC) followed by radiation (RT) represents an evidence-based alternative to CRT albeit its efficacy seems to be inferior to CRT [3].

Based on the above considerations, the combination of IC and CRT was tested with the purpose of overcoming the results achieved with CRT. In this context, two randomized trials failed to show any advantage of this approach over CRT alone, but a significant increase of toxicity [4, 5]. Cetuximab combined with radiotherapy (BRT) was shown to be more effective than radiotherapy alone in LASCCHN patients [6]. Intriguingly, toxicity of BRT was similar to that of radiotherapy alone. Therefore, IC followed by BRT (IBRT) might represent a promising alternative to CRT.

The present paper reports the results of the INTERCEPTOR trial, aimed at evaluating the efficacy of IBRT when compared to standard CRT.

Materials and Methods

This is a phase III multicenter randomized trial designed to compare IBRT (Arm A) versus CRT (Arm B) in patients with LASCCHN (stage III-IV) (Fig. 1). Any patient with a squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx and larynx that met all the inclusion criteria, and none of the exclusion criteria, was eligible for the study. Major inclusion criteria were age ≥18 years, histologically proven SCC of the oral cavity, oropharynx, hypopharynx or larynx; ECOG performance status <2; AJCC stage III or IV; HPV status was not required. In addition, patients had to have adequate renal, cardiac and liver function and normal hematologic blood count.

To be eligible for the study, patients had to be considered unresectable by the referral ENT surgeon. Patients with resectable tumors could also be considered eligible if the patient refused surgery.

Treatments

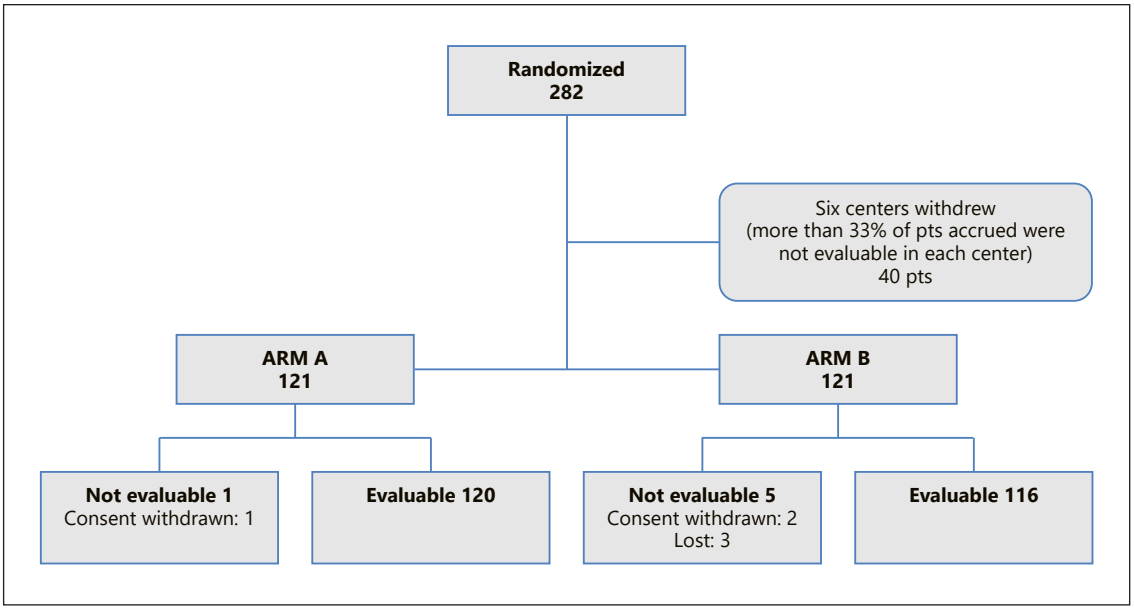
The TPF regimen developed by Vermorken et al. [7] was the IC selected for the experimental arm: docetaxel (T), 75 mg/m^2 day 1, cisplatin (P), 75 mg/m^2 day 1 and FU (F), 750 mg/m^2 days 1–5. Prophylactic granulocyte colony-stimulating factor and antibiotics during TPF were allowed. TPF was followed by BRT 3 weeks after the third course of TPF. The first cetuximab administration was given as loading dose of 400 mg/m^2 1 week before BRT.

Cetuximab was administered at 250 mg/m^2 for 7 weekly doses during radiotherapy. In the reference arm, 3 courses of cisplatin, 100 mg/m^2, were given on day 1 every 3 weeks concurrent with RT [8]. The same RT treatment was given in both arms: 70 Gy, 2 Gy per day, 5 days per week. Intensity-modulated RT and three-dimensional conformal RT were both accepted.

Randomization and Statistical Analysis

The INTERCEPTOR was an open label trial. Randomization was performed phoning centrally to the Clinical Trials Office of the S. Croce Teaching Hospital, and it was stratified by center. Random assignment was done with a 1:1 ratio. Random lists within each stratum were balanced using permuted blocks of varying size, in random order.

The primary endpoint was overall survival (OS), defined as the time from randomization to the last follow-up or death from any cause. Secondary endpoints were progression-free survival (PFS) defined as the time from randomization to local progression, occurrence of distant lesions, progression of existing metastases, death from any cause, or last follow-up, whichever first occurred, incidence of acute or late toxicities (according to the NCI-CTCAE 3) and response rate.



Color version available online

Fig. 2. Consort flow diagram.

Sample Size and Target of the Present Paper

The primary study endpoint was OS. Original sample size estimates were based on an estimated OS of 30% at 3 years in the standard arm (Arm B). Due to miscalculations, in the protocol it was originally estimated that in order to detect, with 80% power at the 5% (2-sided) significance level, an improvement in 3-year OS from 30 to 40%, it was necessary to enroll a total of 278 patients. When these estimates were later revised, it was acknowledged that for detecting with 80% power the above specified absolute increase in 3-year OS, corresponding to a hazard ratio (HR) of 0.76, it was necessary to observe 422 events (deaths). To this aim, it would have been necessary to enroll 511 patients over a 3-year period, and to continue the study for approximately 2.5 years of further follow-up. After 8 years form the start of patient enrollment, 282 patients had been enrolled.

However, there were centers whose performance was grossly inadequate in terms of data provided to the Trial Coordinating Center, with >33% of enrolled patients without any post-randomization case reports form (CRF) having been filled in. In order to avoid any bias, it was decided to exclude from all the analyses all the 40 patients recruited by these centers, including those patients for whom only limited post-randomization information was available. This left 242 patients available for the analyses. Six patients were lost to follow-up (2 in Arm A and 4 in Arm B), but information on their survival was obtained by the general register office.

Due to the long time since the study start, and to the fact that patient enrollment was very slow, it was decided to proceed with an unplanned interim futility analysis. Futility analyses are widely used to assess if a study can be concluded because its interim results allow investigators to rule out, with adequate confidence, the possibility that, even if continued to its planned end, the study could provide a positive result. However, they do not allow a positive result (i.e., that there is a significant difference) to be declared. As such, they do not need to be planned in advance, nor do they require a correction for multiple testing of the significance levels.

The statistical software used was SPSS Statistics version 17.

Results

Recruitment and Evaluable Patients

Twenty centers obtained the approval from the Ethical Committee but only 16 of them enrolled patients into the INTERCEPTOR study. Accrual per year was much slower than expected and between September 2009 and December 2016, 282 patients were recruited. Nine centers recruited 90% of patients enrolled (255/282); 2 centers recruited more than 50% of the whole population. In addition, six centers had more than 33% non-evaluable patients and were excluded from all analyses. The 10 remaining centers accrued 242 patients, of whom 236 were evaluable for OS. The consort diagram (Fig. 2) reports the reasons for exclusion from the analysis. Overall, only 84% of the randomized patients were evaluable.

Patient and Tumor Characteristics

The relevant characteristics of the 236 patients evaluable for survival were balanced between the two treatment arms (Table 1). Overall, 159 T3–T4 patients and 187

Table 1. Patient and tumor characteristics: the major patients' characteristics of the 236 patients evaluable for survival were balanced between the two treatment arms

Patients and tumor characteristics	CR → BRT (Arm A)	CRT (Arm B)	Total
Male/Female	99/21	93/23	192/44
PS 0/1	93/21	83/33	176/54
T1	7	7	14
T2	40	23	63
T3	32	31	63
T4	41	55	96
N0	12	14	26
N1	12	11	23
N2	84	81	165
N3	12	10	22
STAGE II/III/IV	1/13/106	0/10/106	1/23/212
Oropharynx	64	59	123
Hypopharynx	35	34	69
Oral cavity	9	5	14
Larynx	12	18	30
Median age, years	59 (45–79)	60 (48–76)	59.5
Smokers and former smokers (>10 patient-years)	97	101	198
Smokers and alcohol addicts	54	52	106

Table 2. Compliance with medical treatment

	CT → BRT (Arm A) (%)	95% CI	CRT (Arm B) (%)	95% CI
Planned courses of CT	103 (86%)[2]	0.80–0.92	92 (79%)[1]	0.72–0.87
2 courses of CT	5		14	
1 course of CT	9		8	
No CT	3		2	
Planned courses of Cet	78 (65%)[3]	0.56–0.74		
5–7 courses of Cet	27			
1–4 courses of Cet	6			
No Cet	9			
Planned courses of Cet and CT	71 (59%)[4]	0.50–0.68		
>33 fractions/2 Gy	103	0.80–0.92	111	0.92–0.99
>50 Gy < 66 Gy	3		4	
IMRT	72	0.51–0.69	71	0.52–0.70
Mean RT dose	68±7.8		69±8.6	
3D	22		23	
3D + IMRT	21		23	
Interruptions	9		2	
Treatment delay	+13.5 days		+8 days	

Cet, cetuximab; IMRT, intensity modulated radiation therapy. 1 vs. 2: p = NS; 1 vs. 3: p = 0.014; 1 vs. 4: p < 0.0008.

N2–N3 patients were recruited. Oropharynx was the main primary site of disease (123 cases). The distribution of oropharynx primary tumors was well balanced between the two arms. Gender, smoking and alcohol consumption habits are also reported in Table 1.

Compliance to Medical Treatment

Compliance to treatment is detailed in Table 2 and Table 3. In Arm B (CRT), 92/116 patients received the 3 planned courses of cisplatin (79%) compared to 103/120 patients who received the three planned courses of induc-

Table 3. Compliance with radiation treatment

RT	Arm A (120)	Arm B (116)
>33 fractions/2 Gy	103	111
>50 Gy < 66 Gy	3	4
IMRT	72	71
Mean RT dose	68±7.8	69±8.6
3D	22	23
3D + IMRT	21	23
Interruptions	9	2*
Treatment delay	+13.5 days	+8 days

* $p < 0.06$ (Yates' correction).

Table 4. Toxicity data on 228 patients

Toxicity	Arm A (115 patients)	Arm B (113 patients)	*p*
WBC G3-4	14	11	NS
Neutropenia G3	10	2	0.04*
Anemia G3	3	3	NS
Mucositis G3-4	48	43	NS
TPN	30	34	NS
Median TPN duration (range), days	7.7 (3–59)	8.9 (3–48)	
Body weight loss G2-3	21	36	0.017
Skin toxicity G2-3	73	42	0.00007
Infection/pneumonitis	6/0	9/2	NS

*Yates' correction.

Table 5. Treatment response

Response	IBRT (Arm A)	95% CI	CRT (Arm B)	95% CI	RO, %	
RC	76	0.55–0.72	74	0.55–0.73	79	76
RP	19		14			
SD	5		4			
PD	11		12			
Early death (toxicity)	4		4			
Lost before first evaluation	5		8			

RC, complete response; RP, partial response; SD, stable disease; PD, progressive disease; IBRT, induction CT→BRT; BRT, cetuximab radiotherapy; CI, confidence interval; RO, response objectives.

tion chemotherapy (86%) (p = NS) or to 78 patients who received the planned course of cetuximab (65%) (p = 0.016) in the experimental arm. Considering the compliance to the whole medical treatment in both arms, it was 100% in 92 patients in Arm A and in 71 patients in Arm B ($p < 0.0008$) (Table 2).

Radiotherapy

Conventional fractionated RT (70 Gy in 7 weeks) plus concomitant high-dose cisplatin or cetuximab was programmed respectively in Arms B and A. Compliance to RT during the combined treatment was higher in Arm B. Overall, 90% of patients received more than 66 Gy. The Mean radiation dose was 68 Gy (standard deviation 7.8) in 103 patients in Arm A and 69 Gy (standard deviation 8.6) in 111 in Arm B. Interruptions were more common on Arm A (9 vs. 2 in Arm B); treatment delay was 13.5 and 8 days respectively in Arm A and B.

Each center followed its own high-standard quality assurance, including all procedures (dose to target volume, minimal dose to normal tissue, minimal exposure of operators) aiming to prevent errors and to give high confidence that patients will receive the prescribed treatment correctly.

Toxicity

Toxicity was reported according to NCI-CTCAE vs 3. We have toxicity data from 228 patients. Table 4 shows the observed G2 or above toxicity reported as the worst toxicity encountered during treatment in each patient.

Severe neutropenia and skin toxicity were significantly more frequent in Arm A ($p = 0.04$ and $p = 0.017$), whilst weight loss was significantly worse in Arm B ($p = 0.017$). We did not observe a significant difference in the incidence of mucositis, low white blood cell count (WBC), anemia, parenteral nutrition and infections between the two arms.

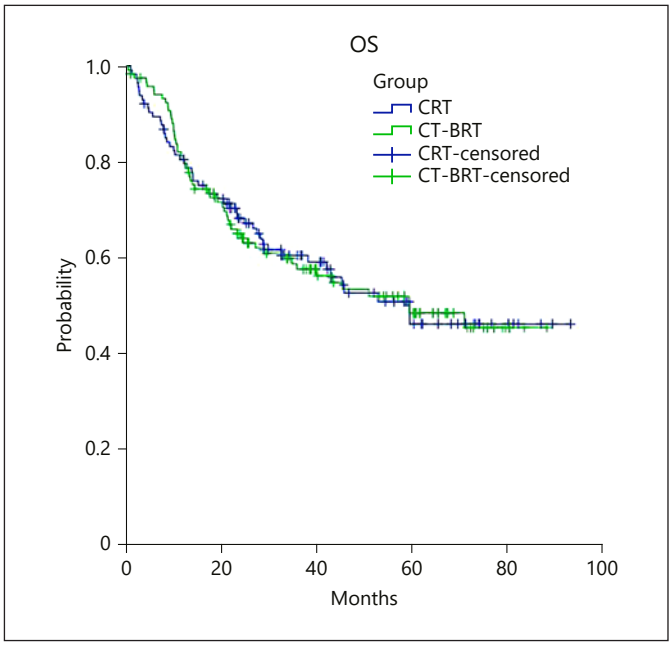
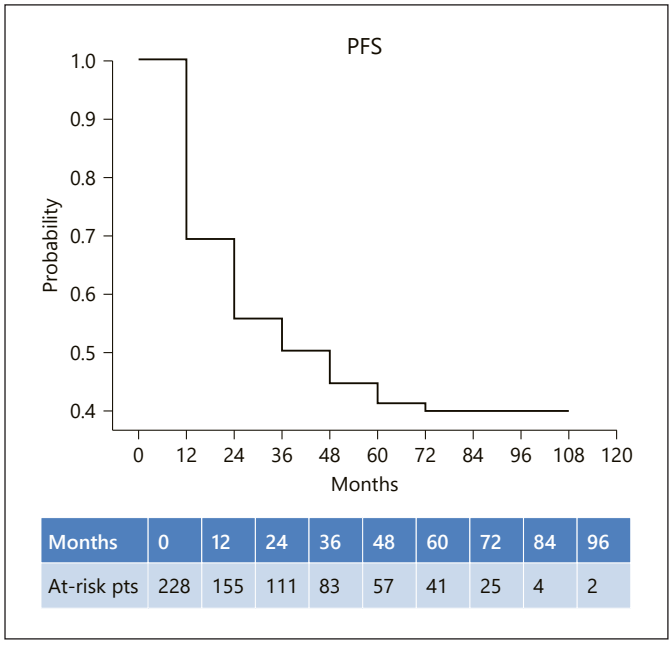


Fig. 3. Overall survival.



Months	0	12	24	36	48	60	72	84	96
At-risk pts	228	155	111	83	57	41	25	4	2

Fig. 4. Progression-free survival.

Response Rate

Response in Arm A and Arm B in the 236 evaluable patients is reported in Table 5. The two treatment arms were associated with comparable response rate 79% (95% CI = 0.55– 0.72) and 76% (95% CI = 0.55–0.73), respectively ($p = 0.47$). Six patients were lost to follow-up before the first response evaluation and were considered failures.

OS and PFS

Survival and PFS analyses by treatment arm are reported in Figure 3 and Figure 4, respectively. Two hundred and twenty-eight patients were evaluated for PFS. OS was similar regardless of the treatment arm (median OS 59 months in both arms), for a HR of 1.05 (95% CI = 0.71–1.54) ($p = 0.8$).

Futility analyses, based on an information fraction of 25% (104/422 events), indicated that the residual power of the study, that is, the probability to detect, at the planned conclusion of the study, a significant difference in favor of the experimental treatment (IBRT) under the alternative hypothesis of HR = 0.76, was 33%. Conversely, the conditional power to detect a significant difference in favor of the standard treatment if this is associated with a HR = 0.76 was 83%.

PFS was similar between the two treatment arms (median PFS 31.6 and 40.3 months in Arm A and B, respectively; $p = 0.48$; HR = 1.03; 95% CI 0.72–1.48).

Discussion

This study was aimed at assessing the efficacy, in LASCCHN, of an experimental regimen based on IBRT, when compared to conventional CRT.

Although the interpretation of our study is greatly hampered by the inadequate number of randomized patients and of observed events, its results suggest that the new regimen is not likely to provide any relevant advantage over the standard regimen, and might indeed be associated with a lower efficacy. In fact, the observed HR of 1.05 (95% CI 0.71–1.54) in favor of the standard regimen significantly decreased (from 80 to 33%) the projected power of the study to detect a 24% decrease in the hazard of death at its planned conclusion.

Furthermore, this result is strikingly similar to that reported by the GORTEC 2007-02 study, which had an identical design, and reported a HR of 1.12 (95% CI 0.86–1.46; $p = 0.39$) in favor of the standard treatment [9]. Overall, when considered together, the results of these two studies strongly argue against the possibility that IBRT might represent a more effective alternative to conventional CRT.

Noteworthy, a worse outcome was seen in patients in the GORTEC study as compared to the present study both in terms of PFS and OS. In the French study the experimental arm (IBRT) was superimposable with Arm A of this study, while standard treatment (Arm B) consisted

of concurrent carboplatin fluorouracil and RT. Median PFS was around 12 months in both arms, which poorly compares to 31.6 and 40.3 months in INTERCEPTOR Arm A and B, respectively. Similarly, median OS was about 24 versus 59 months in both arms, respectively, in the GORTEC and in the INTERCEPTOR study.

However, it must be stressed that the GORTEC study accrued only very advanced stage IV disease and excluded patients with N0, N1 or N2a nodal involvement. The INTERCEPTOR study accrued 23/232 stage III disease and 49/232 patients had N0 or N1 disease.

Considering that the treatments in both arms were the same in the INTERCEPTOR and in the GORTEC 2007-2 study, these large differences confirm the critical role of nodal status in the prognosis of stage IV SCC-HN.

In another perspective, the similarities of the results of the two trials, despite these marked differences in patient characteristics, reinforce the general validity of their negative findings: IBRT should not be considered a new standard of treatment.

Complete response rate at the end of treatment was observed in 63% of patients in both arms. This result is higher than in other studies: in the GORTEC study, Geoffrois et al. [9] reported an 83% disease control rate after induction TPF, but the objective response rate was only 45.5% (CR + PR); in the Intergroup study by Adelstein complete response was identified in 40.2% of the cisplatin-RT patients[8].

Compliance to the medical part of the treatment was better in Arm B.

By considering only chemotherapy there is no significant difference between the two arms, the adherence to the whole planned drug scheduling was significantly worse in Arm A. We could speculate that the more complex and long treatment (Arm A) has more chance to deviate from the original scheduling mainly, but not only, because of toxicity.

We observed marked differences in toxicity such as hematologic and skin toxicities (favoring Arm B) and body weight loss (favoring Arm A), but similar regarding the other major toxicities. The high frequency of febrile neutropenia was also confirmed in the ECRIPS study [10]. Additionally, in our population about 90% of patients were smokers or former smokers. This may impact on both compliance (more mucosal toxicity) and outcomes.

Conclusions

In conclusion, in line with the results reported by the GORTEC group, we failed to find any noteworthy difference in PFS, loco-regional control (LRC) and OS between the two arms; we also confirm a potential TPF-related toxicity and a lower compliance to BRT. We observed a strong difference in the accrual of patients as well as in the quality of data among the participating centers. These differences seem related to the number of patients enrolled by center and to the expertise of the local investigators. Other groups have already observed this correlation [11, 12]. A detailed analysis of this topic is matter of a recently published second paper [13].

Acknowledgments

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Statement of Ethics

Patients have given written informed consent for study trial. Ethical approval was given by local committee on July 17, 2009 (PU01/09-2009/013402-14). Patients signed their written informed consent to the study protocol. The Ethical Committee approved the study and all the patients signed an informed consent before randomization. Our research complies with the guidelines for human studies and the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Disclosure Statement

All authors except M.M., L.L. and M.B. have nothing to declare; M.M. and L.L. worked as consultants for MSD, BMS, Merck; M.B. worked as consultant for BMS.

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There was no funding for research.

Author Contributions

M.M., N.D., E.R.: conception, data collection and processing analysis and interpretation writing and critical review.

M.M., N.D., P.C., M.B., A.B.: data collection literature review.

N.D., P.C., S.V., A.B., P.B.: data collection and processing, analysis and interpretation, critical review.

M.M., L.L., G.N., E.R., R.C.: critical review.

References

1 Argiris A, Harrington KJ, Tahara M, Schulten J, Chomette P, Ferreira Castro A, et al. Evidence-Based Treatment Options in Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck. Front Oncol. 2017 May 9;7:72

2 Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet. 2000 Mar 18; 355(9208):949–55.

3 Pignon JP, le Maître A, Maillard E, Bourhis J; MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol. 2009 Jul;92(1):4–14.

4 Cohen EE, Karrison TG, Kocherginsky M, Mueller J, Egan R, Huang CH, et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. J Clin Oncol. 2014 Sep 1;32(25):2735–43.

5 Haddad R, O'Neill A, Rabinowits G, Tishler R, Khuri F, Adkins D, et al. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. Lancet Oncol. 2013 Mar;14(3):257–64.

6 Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006 Feb 9; 354(6):567–78.

7 Vermorken JB, Remenar E, van Herpen C, Gorlia T, Mesia R, Degardin M, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med. 2007 Oct 25;357(17):1695–704.

8 Adelstein DJ, Li Y, Adams GL, Wagner H Jr, Kish JA, Ensley JF, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol. 2003 Jan 1;21(1):92–8.

9 Geoffrois L, Martin L, De Raucourt D, Sun XS, Tao Y, Maingon P, et al. Induction Chemotherapy Followed by Cetuximab Radiotherapy Is Not Superior to Concurrent Chemoradiotherapy for Head and Neck Carcinomas: Results of the GORTEC 2007-02 Phase III Randomized Trial. J Clin Oncol. 2018 Jul 17:JCO2017762591.

10 Zenda S, Ota Y, Kiyota N, Okano S, Fujii M, Kitamura M, et al. A Multicenter Phase II Trial of Docetaxel, Cisplatin, and Cetuximab (TPEx) Followed by Cetuximab and Concurrent Radiotherapy for Patients With Local Advanced Squamous Cell Carcinoma of the Head and Neck (CSPOR HN01: ECRIPS Study). Front Oncol. 2019 Jan 22;9:6.

11 Bossi P, Miceli R, Benasso M, Corvò R, Bacigalupo A, Sanguineti G, et al. Impact of treatment expertise on the outcome of patients with head and neck cancer treated within 6 randomized trials. Head Neck. 2018 Dec; 40(12):2648–56.

12 Naghavi AO, Echevarria MI, Strom TJ, Abuodeh YA, Venkat PS, Ahmed KA, et al. Patient choice for high-volume center radiation impacts head and neck cancer outcome. Cancer Med. 2018 Oct;7(10):4964–79.

13 Merlano M, Denaro N, Benasso M, Licitra L, Bossi P, Locati L, et al. Difficulties in conducting pure academic research, obstacles in data collection and quality of informations: The example of the INTERCEPTOR study. Oral Oncol. 2019 Oct;97:99–104.