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Impact of the treating institution on the survival of patients with head and neck cancer treated with concomitant alternating chemotherapy and radiation

M. Benasso[a,*], R. Lionetto[b], R. Corvò[c], A. Ponzanelli[a], V. Vitale[c], R. Rosso[a]

[a]*Department of Medical Oncology A, National Institute for Cancer Research, Largo Rosanna Benzi 10, 16132 Genoa, Italy*
[b]*Health Direction—Statistics, National Institute for Cancer Research, Largo Rosanna Benzi 10, 16132 Genoa, Italy*
[c]*Department of Radiation Oncology, National Institute for Cancer Research, Largo Rosanna Benzi 10, 16132 Genoa, Italy*

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Abstract

The aim of this study was to investigate the possible impact of the treating institution on the survival of patients with advanced squamous cell carcinoma of the head and neck treated with radiotherapy alone or concomitant alternating chemotherapy and radiation. The National Institute for Cancer Research of Genoa (IST) was the coordinator of two multicentre randomised trials comparing an alternating chemotherapy and radiation approach to radiotherapy alone with standard fractionation (HN-8 trial: 157 patients) or accelerated fractionation (HN-9 trial: 136 patients) in patients with advanced squamous-cell carcinoma of the head and neck. A single database of the two studies was created and a univariate analysis was performed. The Cox regression model, adjusted for the effect of other prognostic factors, was used to test the impact of the treating institution on survival. Three-year overall survival was 46% for patients treated with chemotherapy and radiation at the coordinating centre and 27% for those treated with the same approach at the affiliated centres ($P = 0.0001$). No difference was detected between patients treated with radiation alone at the coordinating centre or outside (23% versus 21%: $P = 0.52$). The hazard ratio of death for patients treated at the affiliated centres with concomitant alternating chemotherapy and radiation was 2.15 (95% Confidence Interval (C.I.) 1.45–3.18), while it was 1.003 (95% C.I. 0.65–1.55) for those treated with radiation alone. In our experience, the treating institution had a significant impact only on the prognosis of patients treated with the multidisciplinary approach. This finding has implications, both in terms of clinical research and clinical practice.

Keywords: Head and neck; Alternating chemotherapy and radiation; Treating institution; Outcomes

1. Introduction

On the basis of the results of several randomised trials and one meta-analysis based on individual data, concomitant (simultaneous or alternating) chemotherapy and radiation is now considered the treatment of choice in advanced squamous-cell carcinoma of the head and neck and a reasonable alternative to front-line radical surgery in operable laryngeal and hypopharyngeal tumours [1]. Combined alternating chemotherapy and radiation, however, is often hampered by increased acute toxicity that may compromise the treatment delivery with a possible negative impact on the treatment efficacy. As a consequence, for patients with locally advanced disease who cannot receive the support necessary for dealing with the effects of more complex and toxic combined therapies, radiotherapy alone is still indicated as the more appropriate treatment [1].

A good training in administering drugs and radiation together, as well as a deep knowledge of treatment-related side-effects and possibilities to prevent and to manage those effects, appear of crucial importance to warrant optimal patient compliance, and to avoid treatment interruptions or dose reductions. To pursue such a goal, a close cooperation of a pool of specialists including medical oncologists, radiotherapists, ear, nose and throat (ENT) surgeons, pain and nutrition specialists is needed. Since the level of experience, as well as the availability of oncological care facilities, may be different among the treating centres, a difference in the

* Corresponding author. Tel.: +39-010-560-0668; fax: +39-010-560-0850.
E-mail address: marco.benasso@istge.it (M. Benasso).

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outcome is also possible. A significant association between the treating institution and prognosis has already been shown in the treatment of patients with breast [2] and non-seminoma tumours [3]. However, in head and neck cancer, a clear correlation has not yet been demonstrated.

2. Patients and methods

Between 1987 and 1998, the National Institute for Cancer Research of Genoa (IST) coordinated two consecutive, multicentre randomised trials in head and neck cancer (HN-8 and HN-9 trials). In both trials, the main eligibility criteria were: histologically-confirmed squamous-cell carcinoma of the oral cavity, pharynx (except undifferentiated carcinoma of the nasopharynx) or larynx; stage III or IV disease without distant metastases; age up to 75 years; performance status up to 3, according to the scale of the Eastern Cooperative Oncology Group (ECOG).

A detailed description of the trials, as well as the results have already been reported in Refs. [4,5].

In the HN-8 trial, 157 patients were randomly allocated to receive definitive radiation alone (2 Gy per fraction, one fraction per day, 5 days per week) to a total planned dose of 70 Gy, or four cycles of chemotherapy (weeks 1, 4, 7 and 10) alternating to three courses of radiation (20 Gy each, weeks 2–3, 5–6 and 8–9) to a total planned dose of 60 Gy. Chemotherapy consisted of Cisplatin, 20 mg/m^2/day and 5-fluorouracil, 200 mg/m^2/day, bolus, both given intravenously (i.v.) for 5 consecutive days.

In the HN-9 trial, 136 patients were randomised to receive partly accelerated radiotherapy alone with a final concomitant boost technique (75 Gy/40 fractions in 6 weeks) or the same alternating chemotherapy and radiation regimen given in the HN-8 trial.

Patients were enrolled and treated in nine different institutions in Italy. Considering that the level of experience in alternating chemotherapy and radiation treatments was different between the coordinating centre, where the initial pilot studies were carried out, and the other institutions participating in the two studies, and that most of the affiliated institutions showed different characteristics from those of the coordinating centre with respect to the availability of oncological care facilities, we wanted to test the hypothesis that the treating institution could have played a role in the modulation of the treatment outcomes, particularly for the patients treated with the multidisciplinary approach. Since the patients enrolled in the two studies had to meet the same inclusion and evaluation criteria, all the available information was included in a single database. All the affiliated institutions were pooled into a single group (OUT) and were compared to the coordinating centre (IST). Patients' and tumours' characteristics by treating centre are reported in Table 1.

Survival curves were drawn by the Kaplan–Meier method [6] and were calculated from the date of randomisation to the date of death from any cause. Comparisons were made with the log-rank test [7].

The Cox regression model [8] was used to test the effect of a set of variables on survival and was run with a backward procedure and based on the likelihood ratio test. Variables were all categorical. Trial, gender, age at diagnosis, performance status, site of the primary tumour, size of the tumour, nodal involvement, stage of disease and treating institution were analysed in the model. In the first model, the variable 'treatment' was included as a stratification factor. In a second model, the analysis was split into two parts: one for patients

Table 1
Patients' characteristics

	IST	OUT	Total	
	n (%)	*n* (%)	*n*	*P* value (df)
Trial				
HN-8	65 (39)	92 (72)	157	0.0001 (1)
HN-9	101 (61)	35 (28)	136	
Gender				
Male	144 (87)	108 (85)	252	
Female	22 (13)	19 (15)	41	0.67 (1)
Site				
Nasopharynx	19 (11)	6 (5)	25	0.009 (4)
Oropharynx	55 (33)	50 (39)	105	
Oral cavity	36 (22)	37 (29)	73	
Larynx	26 (16)	7 (6)	33	
Hypopharynx	30 (18)	27 (21)	57	
T				
2	28 (17)	19 (15)	47	
3	37 (22)	57 (45)	94	
4	101 (61)	51 (40)	152	0.0004 (1)[a]
N				
0	36 (22)	47 (37)	83	
1	27 (16)	26 (20)	53	
2	63 (38)	23 (18)	86	0.006 (1)[b]
3	40 (24)	31 (24)	71	
P.S.				
0	78 (47)	57 (45)	135	
1	88 (53)	70 (55)	158	0.73 (1)
Stage				
3	25 (15)	37 (29)	62	
4	141 (85)	90 (71)	231	0.003 (1)
Age (years)				
⩽60	88 (53)	65 (51)	153	
>60	78 (47)	62 (49)	140	0.75 (1)

df, degree of freedom of Chi square test; IST, coordinating centre; OUT, affiliated centres; T, tumour size; *N*, nodal status; P.S., Performance Status according to World Health Organization (WHO) scale.

[a] *T*2-3 versus *T*4.

[b] *N*0-1 versus *N*2-3.

treated with radiotherapy only, and one for patients treated with the combined regimen only.

3. Results

Overall, 166 patients were treated at the coordinating centre (87 with alternating chemotherapy and radiation and 79 with radiation alone) and 127 at the affiliated centres (63 with alternating chemotherapy and radiation and 64 with radiation alone). Four of the affiliated centres treated less than 6 patients while between 24 and 36 patients were treated by each of the remaining four institutions.

Three-year overall survival was 35% (95% Confidence Interval (C.I.) 32–38%) for patients treated at the coordinating centre and 24% (95% C.I. 22–26%) for those treated at the affiliated centres ($P = 0.001$). Three-year overall survival was 46% (95% C.I. 41–51%) for patients treated with alternating chemotherapy and radiation at the coordinating centre and 27% (95% C.I. 24–30%) for those treated with the same alternating chemotherapy and radiation at the affiliated centres ($P = 0.0001$) (Fig. 1), while it was 23% (95% C.I. 21–25%) for patients treated with radiation alone at the coordinating centre and 21% (95% C.I. 19–23%) for those treated with radiation alone at the affiliated centres ($P = 0.52$) (Fig. 2).

The Cox regression analysis stratified for treatment and adjusted for the effects of other variables (Table 2), indicated that the hazard ratio of death for patients treated at the affiliated centres was increased by a factor of 1.48 compared with those treated at the coordinating centre (95% C.I. 1.12–1.94). Most of this difference is explained by splitting the analysis for the two treatments: the hazard ratio of death for patients treated with concomitant alternating chemotherapy and radiation at the affiliated centres was 2.15 (95% C.I. 1.45–3.18), while it was 1.003 (95% C.I. 0.65–1.55) for those treated with radiation alone.

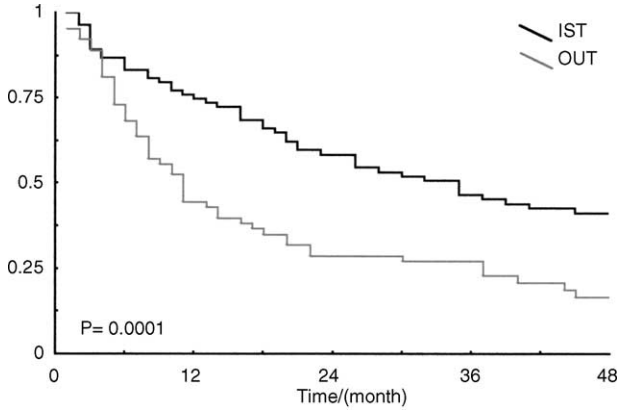

Fig. 1. Overall survival of patients treated with alternating chemotherapy and radiation. IST, coordinating centre (87 patients), OUT, affiliated centres (63 patients).

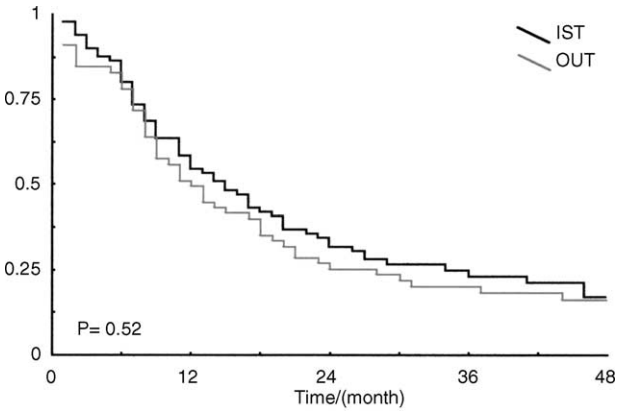

Fig. 2. Overall survival of patients treated with radiotherapy alone. IST, coordinating centre (79 patients), OUT, affiliated centres (64 patients).

The analysis of treatment compliance showed no difference in terms of the dose of radiation actually delivered or treatment delays for patients treated with radiotherapy alone at the coordinating centre or outside.

In the group of patients who received the combined approach, 3% of those treated at the coordinating centre never received chemotherapy versus 10% (3/87 versus 6/63) of those treated at the affiliated institutions; 11% versus 22% (10/87 versus 14/63) had a treatment delay of more than 1 week; the median relative dose intensity of chemotherapy was 82% versus 75%; 10% versus 21% (9/87 versus 13/63) received less than 50 Gy. None of these differences reached statistical significance. The analysis of toxicity limiting the treatment showed no significant differences: 30% of patients treated with the combined approach at the coordinating centre suffered grade III-IV mucositis versus 27% of those treated at the affiliated institutions; 32 versus 27% had grade III-IV haematological toxicities.

4. Discussion

Results from the present analysis clearly indicate that, in this experience, the treating centre played a major role in the outcome of patients treated with concomitant alternating chemotherapy and radiation, while its role was not significant for patients treated with radiation alone.

To understand the factors that contribute to different outcomes in different centres is not easy. The hypothesis that selection factors may contribute to differences is, in our opinion, unlikely because of the strict eligibility criteria used for trials entry and the lack of effect across centres for the radiation alone control arm. Moreover, referral practice was based only on the distance of the patients' residence from the treating centre.

It is interesting that in the group of patients who received the combined approach at the affiliated institutions a greater tendency to give less chemotherapy and radiation and to delay the therapy was observed

Table 2
Overall survival: univariate and Cox regression analyses

	Univariate		Cox regression	
	% at 3 years (95% C.I.)	*P* value (df)	Hazard ratio (95% C.I.)	*P* value (df)
Centre				
IST	35 (32–38)		1	
OUT	24 (22–29)	0.001 (1)	1.48 (1.12–1.94)	0.006 (1)
Trial				
HN-9	33 (30–36)		1	
HN-8	28 (26–30)	0.062 (1)	1.27 (0.94- 1.70)	0.11 (1)
Gender				
Male	29 (27–31)		1	
Female	38 (32–44)	0.617 (1)	0.94 (0.63–1.4)	0.74 (1)
Site				
Nasopharynx	63 (51–75)		1	
Oropharynx	32 (29–35)		1.57 (0.89–2.76)	
Oral cavity	23 (21–25)		2.14 (1.19–3.81)	
Larynx	26 (22–30)		1.63 (0.86–3.08)	
Hypopharynx	23 (20–26)	0.021 (4)	2.08 (1.15–3.78)	0.06 (4)
T				
2	40 (34–46)		1	
3	33 (30–36)		1.27 (0.8–2.02)	
4	26 (24–28)	0.064 (2)	1.32 (0.85–2.07)	0.46 (2)
N				
0	32 (29–35)		1	
1	37 (32–42)		1.26 (0.82–1.95)	
2	30 (27–33)		1.14 (0.72–1.79)	
3	24 (22–26)	0.454 (3)	1.24 (0.79–1.94)	0.7 (3)
P.S.				
0	35 (32–38)		1	
1	26 (24–28)	0.021 (1)	1.21 (0.92–1.60)	0.17 (1)
Stage				
3	47 (41–53)		1	
4	26 (25–27)	0.012 (1)	1.7 (1.15–2.46)	0.007 (1)
Age (years)				
$\leqslant 60$	34 (31–37)		1	
> 60	27 (25–29)	0.145 (1)	1.36 (0.86–1.49)	0.37 (1)
Treatment				
RT	22 (20–24)			
RT + CT	38 (35–41)	0.010 (1)	Stratification factor	

df, degree of freedom of chi square test; IST, coordinating centre; OUT, affiliated centres; T, tumour size; *N*, nodal status; P.S., performance status according to WHO scale; CT, chemotherapy; RT, radiotherapy.

despite the lack of difference in terms of severe treatment-related side-effects. Although none of these factors in itself reaches statistical significance, the combined impact may have been clinically important. The lack of a close interaction among specialists necessary to warrant the optimal support to the patients, as well as the lower expertise with the combined treatment due to the small number of patients treated per year, may explain the more cautious approach in administering the combined treatment in the affiliated centres, leading to the poorer outcomes.

However, a further effect of intrinsic differences between the patient populations, not accounted for in the analysis, cannot be completely excluded. Moreover, results should be interpreted with caution because the comparisons do not come from a prospective randomised study. Unfortunately, a prospective randomised trial addressing the role of the treating centre in the outcomes is clearly not feasible.

In conclusion, the trends and effects revealed in this analysis, if confirmed, may have important implications either in clinical research or in clinical practice.

In clinical research, the influence of the treating centre on outcome may be a serious bias in large, cooperative, randomised trials, particularly when more complicated multidisciplinary treatments are compared with standard therapies. Therefore, a careful selection of the institutions as well as continuous monitoring of the treatment quality is essential. Moreover, in the analysis of the data, the impact of the treating centre should be always investigated.

In clinical practice, alternating chemotherapy and radiation regimens should be administered within institutions that are familiar with the problems related to these treatments, otherwise radiotherapy alone should still be considered the optimal therapeutic option for patients with advanced head and neck cancer.

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