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Cancer of the larynx: the outcomes of conventionally fractionated radiotherapy in prospective and retrospective studies. Is the meaning of conventionality the same?

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Introduction. Two studies on the radiotherapy of laryngeal cancer were completed at the Radiotherapy Department of the Cancer Center Warsaw at the end of 1999. One of them was a multicenter randomized clinical trial, and the second one – a retrospective study on patients treated between years 1989 and 1995. An opinion exists that the trial outcomes of the conventional arm correspond to the outcomes of everyday practice. The subject of the study was to evaluate this thesis, and to find out, whether the outcomes of prospective and retrospective studies following the same treatment protocol are comparable.
Material and methods. Selection criteria were – age ≤75, WHO 0-1, T1, T2, T3, N0, M0 stage of glottic and supraglottic laryngeal cancer. The treatment was: 66 Gy/2 Gy/33 fraction/45 days. The prospective group had – 199 patients, and the retrospective group: 150 patients. The two groups were comparable according to the age, site, sex and mean hemoglobin level. There was a significant difference in T-stage and performance status between the two groups. Overall survival, local control and CR-response were analyzed. To eliminate the influence of the differences in T-stage and performance status, regression models were applied – Cox's for survival and local control, logit for CR-response endpoint.
Results. The protocol compliance (prospective, retrospective) was as follows – total dose: (88%, 49%), treatment time: (47%, 11%) respectivaly. Three-year survival for the prospective and the retrospective groups were 89% and 74%, respectively ($p=0.035$), CR-response rates were 96% and 75%, respectively ($p<0.001$). There were no significant differences in probability of local recurrence in CR patients.
Conclusions. A better outcome of treatment was observed in the prospective study group. It is probably due to a certain "over-selection" of patients for the prospective study and many deviations from the therapeutic protocol in the historical group. "Conventional treatment" has the same meaning in the prospective and retrospective study only as far as the protocol is concerned, but differs in the protocol realization and in the patients selection. However, these observations do not affect the reliability of the clinical trial outcomes. The aim of a clinical trial is to compare two treatment methods – experimental and conventional – in two comparable groups of patients, and the comparability is accomplished by randomization.

Rak krtani: wyniki radioterapii frakcjonowanej konwencjonalnie w badaniu prospektywnym i retrospektywnym. Czy w obu przypadkach określenie konwencjonalnie oznacza to samo?

Wstęp. W końcu 1999 roku w Zakładzie Radioterapii Centrum Onkologii w Warszawie ukończono dwa badania, dotyczące radioterapii chorych na raka krtani: 1. Wieloośrodkowe, randomizowane badanie kliniczne III fazy; 2. Retrospektywna analiza chorych leczonych w Zakładzie Radioterapii w Warszawie w latach 1989-1995. W ramieniu konwencjonalnym randomizowanego badania klinicznego zastosowano metodę leczenia zgodną z obowiązującym protokołem terapeutycznym. Wyniki uzyskane w tym ramieniu powinny być zatem zbliżone do wyników uzyskanych w codziennej praktyce. Celem niniejszej pracy jest sprawdzenie tej tezy.
Materiał i metoda. Kryteria doboru chorych były jednakowe dla obu grup: rak głośni i okolicy nadgłośniowej krtani, wiek ≤75, WHO: 0-1, T1-T3, N0, M0. Leczenie: 66 Gy/2 Gy/33 w ciągu 45 dni. Grupa prospektywna: 199 chorych, historyczna: 150 chorych. Analizowano czas przeżycia, wyleczenie miejscowe i odpowiedź na leczenie. W celu uwzględnienia występujących róż-

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nic w rozkładach cechy T i stopnia sprawności zastosowano modele regresji – Cox'a w analizie przeżycia i miejscowego wyleczenia oraz logitowej w analizie odpowiedzi na leczenie.
Wyniki. Odpowiednio w badaniu prospektywnym i retrospektywnym: zgodność z protokołem – dawka: 88%, 49%, czas leczenia: 47%, 11%; trzyletnie przeżycie: 89% i 74% (p=0,035), odpowiedź na leczenie: 96% i 75% (p<0,001). Nie stwierdzono różnicy w analizie czasu do miejscowego niepowodzenia (dla pacjentów z CR).
Komentarz. Znacznie lepsze wyniki leczenia stwierdzono w badaniu prospektywnym, co najprawdopodobniej jest efektem „nad-selekcji" przypadków do badania prospektywnego. Drugim powodem może być mniejsza dyscyplina przestrzegania protokołu terapeutycznego w grupie historycznej. Określenie „leczenie konwencjonalne" dla obu grup oznacza to samo wyłącznie w odniesieniu do zasad protokołu terapeutycznego. Różni się ono jednak w realizacji protokołu doboru chorych do leczenia. Powyższe spostrzeżenia nie podważają wiarygodności wyniku badania prospektywnego, którego celem było porównanie metod leczenia – eksperymentalnej i konwencjonalnej – w dwóch porównywalnych grupach chorych, co osiągnięto na drodze randomizacji.

Key words: cancer of the larynx, radiotherapy, randomized trial, retrospective study
Słowa kluczowe: rak krtani, radioterapia, badania randomizowane, badania retrospektywne

Introduction

By definition results of clinical randomized studies are relative. They depend on the efficacy of both the "experimental" and the "conventional" arm. Our attention is usually focused on the experimental data, while the results of the conventional arm are considered as the reflection of everyday practice. Proving this thesis is the aim of the study.

At the end of 1999 two studies were finished at the RT Department at the Oncology Center in Warsaw, both concerned the radiotherapy of the laryngeal cancer: one was a multicenter randomized clinical trial (1995-1998) [1], the second, a retrospective study on patients treated in Warsaw from 1989 up to 1995 [2]. The treatment protocols were the same in the conventional arm of the clinical trial and in the retrospective study. This created the opportunity for comparing the outcomes in the conventional arm of the clinical trial with the results of standard treatment.

Aim of the study

To define the differences in patient characteristics, compliance to protocol, early morbidity, response to treatment, local-regional control and survival probability in the "conventionally" treated patients in a prospective and a retrospective study.

Materials and methods

Selection criteria: patients with glottic and supraglottic cancer, age: ≤75, performance status: 0-1, stage: T1 T2 T3 N0 M0. Treatment: 66 Gy/ 2 Gy /33 fractions /45 days. Material: prospective group: 199 patients, retrospective group: 150 patients. Endpoints: tumor response was assessed at the end of radiotherapy, 4 weeks, and 8 weeks after treatment completion. It was recorded as complete regression, partial regression or no response. The endpoints were loco-regional control, disease-free survival and overall survival. Dosimetry: Physicists performed beam dosimetry. Preparation for treatment included the following steps:

- The patient was placed in supine position in a thermoplastic mould with a head-support to keep the cervical spine parallel to the couch.
- Radiograms of the portal were taken on simulator; the tumor site was marked (including individual shielding if necessary).
- The contour has been taken in the central plane of fields for the first and second stage of treatment. In T3 glottic and supraglottic cancer the contour was taken in two planes. The target and the spine were marked in both stages of treatment (in supraglottic and glottic T3 first step of treatment encompassed the larynx and, electively, the cervical nodes).
- The dose was estimated at the reference point (ICRU 50).

Statistical methods

Patient characteristics, compliance with protocol, early morbidity and response to treatment were analysed for both studies by statistical descriptive methods. The overall survival and the local recurrence free probability (LRFP) were calculated with the Kaplan-Meier methods [3]. LRFP was defined only for patients with complete regression (CR) treatment response. The treatment response was assessed two months after the onset of the radiotherapy. Loco-regional control (LC) was calculated by the multiplication of LRFP by the CR-response probability. To eliminate the influence of the differences in patient characteristics the regression models were applied – Cox's proportional hazard model for death and local recurrence endpoints [4], logit model for CR-response endpoints [5].

Results

The prospective and retrospective study groups were comparable according to age, site, sex and mean hemoglobin level (Tab. I). There was a significant difference in T-stage and performance status between two groups (Tab. II). The analysis of compliance with the protocol (Tab. III) showed differences in the total dose and the total time. The treatment course was in much better compliance with the protocol in the prospective study. Severe symptoms of early morbidity were more frequently recorded in the prospective group while some 8-12% of data concerning early toxicity was missing in the retrospective group (Tab. IV).

The response to treatment (Tab. V) was about 20% higher in the prospective group, both when compared for the entire group and in the particular T stages.

Survival probability analysis indicated better life prognosis in the 'clinical-trial' group of patients (Fig. 1, Tab. IX).

Tab. I. The pretreatment characteristics of the "prospective" and "retrospective" study groups

	Prospective study N=199	Retrospective study N=150
Age		
≤55	73 (37%)	52 (35%)
≥55	126 (63%)	98 (65%)
Site		
glottic	148 (74%)	110 (73%)
supraglottic	51 (26%)	40 (27%)
Sex		
female	30 (15%)	15 (10%)
male	169 (85%)	135 (90%)
WHO		
0	177 (89%)	107 (71%)
1	22 (11%)	43 (29%)
T stage		
T1	93 (47%)	51 (34%)
T2	85 (43%)	58 (39%)
T3	20 (10%)	41 (27%)
missing data	1	0
Hemoglobine		
(min, max)	(8.6, 17.3)	(8.2, 17.4)
mean (std. deviation)	14.4 (1.4)	14.0 (1.8)

Tab. II. T stage in glottic and supraglottic cancer

GLOTTIC	Prospective study N=148	Retrospective study N=110
T stage		
T1	85 (58%)	43 (39%)
T2	52 (35%)	48 (44%)
T3	10 (7%)	19 (17%)
missing data	1	0
Supraglottic	N=51	N=40
T stage		
T1	8 (16%)	8 (20%)
T2	33 (63%)	10 (25%)
T3	10 (20%)	22 (55%)

Tab. III. Compliance to protocol

	Prospective study N=199	Retrospective study N=150
Overall dose		
2100 – 5799	0	4 (2.5%)
5800 – 6399	0	6 (4%)
6400 – 6599	1 (0.5%)	13 (9%)
6600 (according to protocol)	175 (88%)	74 (49%)
6601 – 6800	14 (7%)	15 (10%)
6801 – 7000	1 (0.5%)	16 (11%)
7001 – 7200	8 (4%)	18 (12%)
7201 – 7400	0	4 (2.5%)
Overall treatment time		
- 2 or more days	0	9 (6.5%)
-1 day	3 (1.5%)	13 (9%)
according to protocol (45 days)	94 (47%)	17 (11%)
+ 1-7 days	87 (44%)	73 (55%)
+ 8-14 days	6 (3%)	20 (13%)
+ 15-21 days	7 (3%)	8 (5.5%)
+ 21 days or more	2 (1%)	0
Other primary carcinoma	1 (0.5%)	10 (7%)
missing data	0	5

Tab. IV. Early toxicity (at the very end of treatment)

	Prospective study N=199	Retrospective study N=150
Pain on swallowing		
none	19 (10%)	55 (39%)
severe	180 (90%)	87 (61%)
missing data	0	8
Dysphagia		
none	26 (13%)	72 (52%)
slight	117 (59%)	58 (42%)
severe	56 (28%)	8 (6%)
not applicable	1 (0.5%)	-
missing data	0	12
Need for analgesia		
none	73 (37%)	96 (76.2%)
local analgesia	56 (28%)	22 (17.5%)
general analgesia	69 (35%)	7 (5.5%)
narcotics	1 (0.5%)	1 (0.8%)
missing data	0	24
Mucositis		
none	27 (14%)	14 (10%)
patchy mucositis	61 (31%)	71 (51%)
confluent mucositis	111 (56%)	54 (39%)
missing data	0	11

Tab. V. Response to treatment (3 months after the start of treatment)

Tumor regression	Prospective study N=199	Retrospective study N=150
all cases		
not CR	7 (3.6%)	37 (24.7%)
CR	187 (96.4%)	113 (75.3%)
95%CI for CR	(93.7%, 99.1%)	(68.3%, 82.3%)
missing data	5	0
T1		
not CR	4 (4.5%)	10 (19.6%)
CR	84 (96.5%)	41 (80.4%)
95%CI for CR	(92.6%, 100%)	(69.2%, 91.6%)
missing data	5	0
T2		
not CR	2 (2%)	12 (20.7%)
CR	83 (98%)	46 (79.3%)
95%CI for CR	(95%, 100%)	(68.7%, 89.9%)
T3		
not CR	1 (5%)	15 (36.5%)
CR	19 (95%)	26 (63.4%)
95%CI for CR	(85.3%, 100%)	(48.4%, 78.4%)

There were no significant differences in the time to local recurrence curves (patients with CR) (Fig. 2, Tab. X). The LC curves reflect the differences in the CR response rate (Fig. 3).

Because of the differences in the T-stage and the performance status these two factors were included as the coefficients with the treatment group indicator to the logit and proportional hazard Cox's models. The regression models confirmed better life prognosis and treatment response for patients from the prospective study (Tab. VI, VII). No differences were found between the groups in the Cox's model analysis with the local recurrence endpoint (CR-cases) (Tab. VIII).

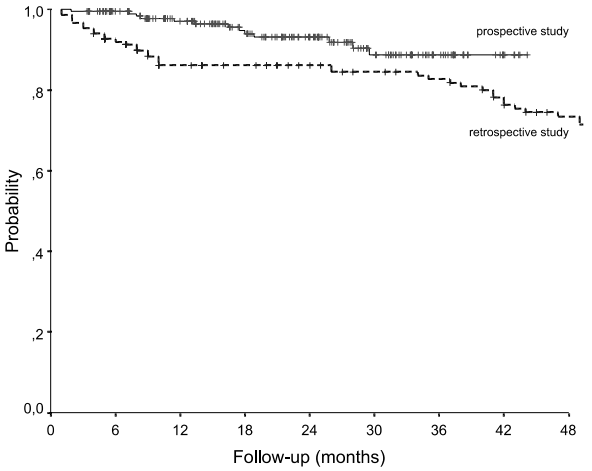

Fig. 1. Probability of survival

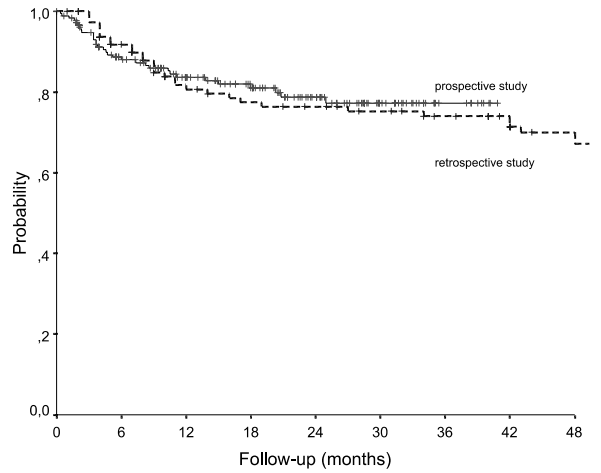

Fig. 2. Local recurence free probability (patients with CR)

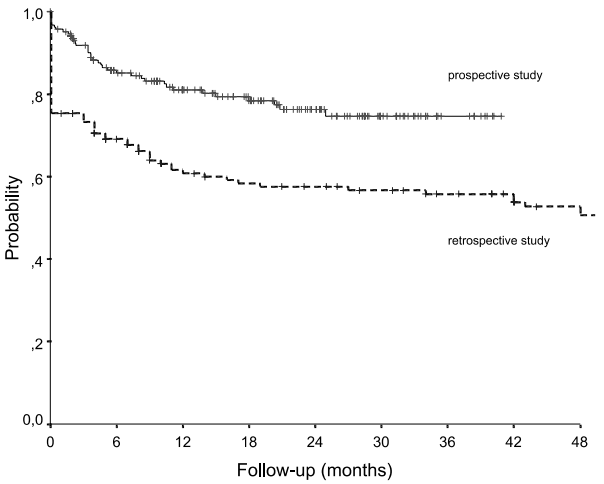

Fig. 3. Loco-regional control for all patients

Comments

Both the response to treatment and local control were about 20% higher in the conventional arm of the prospective study than in the retrospective group. However the 95% response rate in T3 cases and a few percent higher in T1 and T2 cases is unusual in everyday practice. The interpretation of the outcomes in the prospective study and their significance for clinical practice calls for

Tab. VI. Model coefficients in Cox's regression model for overall survival

	β	s. e. for β	p-value	RR
T (T1)			0.1902	
T2	0.2935	0.2256	0.1932	1.3411
T3	0.4347	0.2536	0.0865	1.5445
WHO (WHO=0)				
WHO=1	-0.0540	0.2942	0.8543	0.9474
group (prospective)				
retrospective	0.7301	0.3468	0.0353	2.0754

Tab. VII. Model coefficients in logistic regression model for CR

	β	s. e. for β	p-value	OR
T (T1)			0.0847	
T2	0.1824	0.4253	0.6681	1.2000
T3	0.7366	0.4355	0.0901	0.4787
WHO (WHO=0)				
WHO=1	0.4474	0.4322	0.3006	1.5642
group (prospective)				
retrospective	-2.2644	0.4666	<0.0001	0.1039

Tab. VIII. Model coefficients in Cox's regression model for local recurence endpoint

	β	s. e. for β	p-value	RR
T (T1)			<0.0001	
T2	1.0688	0.3441	0.0019	2.9119
T3	2.0732	0.3615	<0.0001	7.9505
WHO (WHO=0)				
WHO=1	0.4292	0.3080	0.1636	1.5360
group (prospective)				
retrospective	-0.2398	0.2778	0.3880	0.7868

Tab. IX. Overall survival

Cumulative probability ±SE	Prospective study N=199	Retrospective study N=150
all cases		
12 months	0.97 ± 0.03	0.86 ± 0.06
24 months	0.93 ± 0.06	0.84 ± 0.06
36 months	0.89 ± 0.11	0.74 ± 0.06
T1		
12 months	0.98 ± 0.02	0.92 ± 0.08
24 months	0.90 ± 0.05	0.92 ± 0.08
36 months	0.90 ± 0.05	0.90 ± 0.09
T2		
12 months	0.96 ± 0.04	0.87 ± 0.09
24 months	0.94 ± 0.06	0.87 ± 0.09
36 months	0.90 ± 0.10	0.85 ± 0.10
T3		
12 months	1.00 ± 0.45	0.76 ± 0.14
24 months	1.00 ± 0.45	0.76 ± 0.14
36 months	0.85 ± 0.38	0.69 ± 0.16

Tab. X. Local recurrence free probability (patients with CR)

Loco-regional control probability	Prospective study N=199	Retrospective study N=150
all cases		
12 months	0.84 ± 0.07	0.84 ± 0.06
24 months	0.79 ± 0.11	0.78 ± 0.07
36 months	0.77 ± 0.23	0.76 ± 0.07
T1		
12 months	0.85 ± 0.08	0.94 ± 0.06
24 months	0.81 ± 0.09	0.87 ± 0.10
36 months	0.81 ± 0.09	0.87 ± 0.10
T2		
12 months	0.83 ± 0.10	0.86 ± 0.10
24 months	0.78 ± 0.11	0.82 ± 0.11
36 months	0.74 ± 0.13	0.82 ± 0.11
T3		
12 months	0.82 ± 0.18	0.61 ± 0.16
24 months	0.69 ± 0.29	0.61 ± 0.16
36 months	0.69 ± 0.29	0.52 ± 0.18

careful consideration. A certain 'overselection' of patients for the clinical trial, more exact compliance with the protocol and better quality documentation were probably the main reasons of the incomparability of the results in the two compared studies. Outcomes of the clinical trial are, basically, of scientific significance. However they present evidence based suggestions concerning new possibilities – how to improve treatment efficacy within the limits of acceptable morbidity. The clinical trial analyzed simultaneously with the retrospective study allow for a comprehensive approach to the scientific and practical problems of the radiotherapy of laryngeal cancer. Exact compliance with the treatment protocol and the avoidance of overall treatment prolongation may positively influence treatment outcomes without changing the fractionation schedule. Comprehensive data concerning patients not entered into the trial and about patients not qualified for treatment in everyday practice would supply additional information concerning the value of both forms of clinical studies.

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