The effect of addition of chemotherapy to radiotherapy in the treatment of women with cervical cancer: A survival analysis using propensity score

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Abstract

Objective. To compare the overall survival of patients with cervical cancer treated exclusively with radiotherapy with that of patients treated with a combination of radio and chemotherapy.

Material and methods. Retrospective analysis of all cases of cervical cancer registered at the Brazilian National Cancer Institute between 1999 and 2004, treated with radiotherapy exclusively or in combination with chemotherapy. The Kaplan–Meier curve and the log-rank test were used to assess overall survival. The Cox model and the propensity score were used for multivariate analysis.

Results. A total of 2584 patients were studied, and the clinical and epidemiological characteristics of the cohort were described. The combination of chemotherapy with radiotherapy provided an improvement in survival when compared with radiotherapy exclusively (HR-0.69; $p < 0.001$), which persisted after multivariate analysis (HR-0.72; $p < 0.001$).

Conclusion. There was a beneficial effect of adding chemotherapy to radiotherapy on this cohort.

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Keywords: Cervical cancer; Epidemiology; Survival analysis; Radiotherapy; Chemotherapy

Introduction

Until the end of the last decade, the use of combined chemotherapy and radiotherapy for the treatment of women with cervical cancer was still uncertain and there were a lot of controversy considering improvements in overall survival [1]. At that time, usual therapeutic modalities for curative treatment of that malignancy were surgery and/or radiotherapy [2]. In the early 1990's, several trials [3] studied the association of those modalities with neoadjuvant or concomitant chemotherapy regimens, but the results were negative [4,5].

In 1999, an alert of the North American National Cancer Institute (NCI) drew attention to the publication of five randomized trials concerning the concomitant use of cisplatin-based chemotherapy and radiotherapy [7–10]. Theses trials revealed a favorable impact of combined modality in patients FIGO stage IB2 to IVA, increasing overall survival in approximately 30%.

Despite of the worldwide acceptance of those results and the recommendation for the combined treatment modality on guidelines [11], some questions remained unanswered regarding the effectiveness of the therapeutical combination outside controlled trials, mainly after the negative results of a sixth study conducted in Canada [12]. One major discussion point is that staging on those studies was confirmed by invasive surgical procedures and imaging tests that are not recommended by FIGO and not usually performed in clinical practice of third world centers. This could predispose to the appearance of a favored subpopulation, unable to be characterized in the usual medical care of this regions [13,14].

This study represents a retrospective analysis aiming at determining the impact of the combination of chemotherapy and radiotherapy (under uncontrolled conditions and in usual clinical practice) on overall survival of women with cervical cancer diagnosed and treated at Brazilian National Institute of

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Table 1
Clinical and epidemiological characteristics of the groups treated exclusively with radiotherapy or with the combination of radio- and chemotherapy

	Total		Radiotherapy				P value of χ^2 test
			Exclusive		Combined with chemotherapy		
	n	%	n	%	n	%	
Age							
<30 years	76	100.0	36	47.4	40	52.6	<0.001 *
30–54 years	1399	100.0	1008	72.1	391	27.9	
55–64 years	532	100.0	423	79.5	109	20.5	
≥65 years	531	100.0	454	85.5	77	14.5	
Race							
White	1378	100.0	1048	76.1	330	23.9	0.598
Non-white	1159	100.0	871	75.2	288	24.8	
Educational level							
Illiterate	522	100.0	441	84.5	81	15.5	<0.001 *
<8 years	1282	100.0	957	74.6	325	25.4	
8 years	536	100.0	400	74.6	136	25.4	
≥11 years	196	100.0	120	61.2	76	38.8	
Histological type							
Squamous cell carcinoma	2189	100.0	1676	76.6	513	23.4	0.008
Others	350	100.0	245	70.0	105	30.0	
Stage							
I	159	100.0	101	63.5	58 **	36.5	<0.001 *
II	1064	100.0	775	72.8	289	27.2	
III	1187	100.0	931	78.4	256	21.6	
IV	129	100.0	114	88.4	15	11.6	
Year of diagnosis							
1999	393	100.0	368	93.6	25	6.4	<0.001 *
2000	456	100.0	419	91.9	37	8.1	
2001	433	100.0	417	96.3	16	3.7	
2002	445	100.0	401	90.1	44	9.9	
2003	424	100.0	234	55.2	190	44.8	
2004	388	100.0	82	21.1	306	78.9	
Time for initiating the treatment							
Up to 30 days after diagnosis	131	100.0	112	5.8	19	3.0	<0.001
31–90 days	1170	100.0	825	42.9	345	55.8	
91–180 days	920	100.0	736	38.3	184	29.8	
≥181 days	318	100.0	248	13.0	70	11.4	

Cohort of women with invasive cervical cancer registered at INCA and diagnosed between 1999 and 2004.
 * χ^2 test for trend.
** 57 in stage IB.

Cancer (INCA). Clinical and epidemiological characteristics of the analyzed cohort were also reviewed.

Materials and methods

Data were obtained from the hospital registry of INCA. We selected all cases of non-metastatic cervical cancer diagnosed between 1999 and 2004 that received radiotherapy with or without chemotherapy as a first-line curative intention. To reduce occasional confounding, all patients undergoing surgery or any other type of treatment were excluded.

In this study, the following variables were analyzed: (1) age; (2) year of diagnosis; (3) educational level; (4) race; (5) histological type; (6) staging of the tumor; (7) type of treatment initially offered; (8) time elapsed between diagnosis and treatment starting and (9) overall treatment time.

FIGO staging system [15], ranging from I to IV, was used. Age at diagnosis was categorized as follows: <30 years; 30–54 years; 55–64 years; and ≥65 years. Race was classified as white and non-white, and the tumor histological type was classified as squamous cell carcinoma and other types.

To estimate survival, all deaths in the period studied were considered events. Follow-up period of cases were censored at the last hospital visit, finishing in November 2006.

The Kaplan–Meier Curve with log-rank test was used to compare survival in the two treatment-groups. Propensity score was used to control the potential confounding by others variables (staging of the tumor, age, histological type and
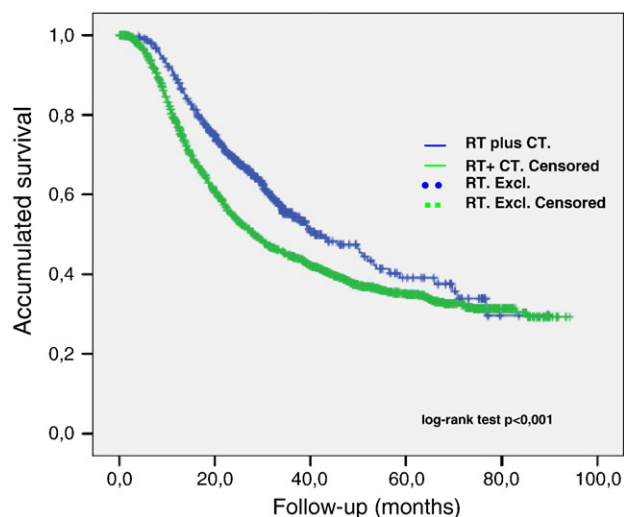
Fig. 1. Non-adjusted Kaplan–Meier curves of the groups treated exclusively with radiotherapy or with the combination of radio- and chemotherapy. Cohort of women with invasive cervical cancer registered at INCA and diagnosed between 1999 and 2004.

educational level) on the outcome. Therefore, those variables were balanced between both groups by means of the estimate (propensity) of being assigned to one or other group of treatment. According to the estimates obtained, five subclasses (quintiles), homogeneous in regard to the chance of undergoing the treatment, were created, allowing comparison between the groups studied and minimizing confounding.

Cox proportional hazards model was used to compare time variable in each subclass originated from the propensity score. The case-fatality rate was calculated based on the number of deaths per person-time (incidence density) in each group of treatment. The chi-square test was used to calculate the statistical significance of the clinical and epidemiological differences between the two groups of treatment.

Results

For this study, 2584 cases were selected, 46 of which were excluded due to lack of important data for the analysis.

Table 1 shows the distribution of the variables available according to the type of treatment applied. Considering all analyzed period, combined modality treatment was used in 24.3% of the cohort (617 cases), and a statistically significant trend ($p < 0.001$) towards an increase (specially after 2002) from 6.4% in the beginning of follow-up to 78.9% at the end of period was observed. A significant trend ($p < 0.001$) towards the use of the combined treatment in younger women was also observed, creating an inverse gradient with aging (most patient with less than 30 years received combined modality treatment while only 14.5% of those above 65 years). Educational level was higher among combined modality treatment group ($p < 0.001$), especially when comparing the proportion of illiterates (22.9% vs 131.1%) and people with mores than 11 years of schooling (6.4% vs 12.3%). In addition, a trend ($p < 0.001$) towards using the combined modality treatment in earlier stages was observed, with only 11.6% of the stage IV patients receiving it.

As a rule, time elapsed to beginning treatment was relatively long in this population (median 93 days, IC 95% (77.4 to 102.5)), although it was slightly shorter for CT plus RT. In this way, considering the first 90 days, 58.3% of patients in combined group begun treatment compared to 48.7% in exclusively RT group ($p < 0.001$).

In the other hand, considering overall treatment time, RT group concluded proposed treatment earlier. As a result, 44.5% of patients in RT group finished their treatment in the first 60 days when compared to 25.5% in combined treatment ($p < 0.001$).

Treatment

In this cohort, external-beam megavoltage RT was administered to a clinical target volume that included the primary cancer, uterus, internal iliac, presacral, upper external iliac, and lower common iliac lymph nodes. A dose of 45 Gy was prescribed in 25 equal fractions. Intracavitary brachytherapy followed the external-beam RT (HDR, the dose was 24 Gy in three insertions). CDDP was administered in a dose of 40 mg/m^2 on a weekly basis (maximum allowed 5 cycles), given concurrently with the external-beam RT. Most patients received at least 4 cycles of chemotherapy (76.7%). The main reasons for interrupting cisplatin were renal impairment

Table 2
Subclasses based on the quintiles of the propensity score derived from the probability of being treated with radiotherapy exclusively or in combination with chemotherapy

| Quintiles of the propensity score | Total | | Radiotherapy | | | |
| | | | Exclusive | | Combined with chemotherapy | |
	n	%	n	%	n	%
1 = 0.0005 a 0.0250	506	100.0	499	98.6	7	1.4
2 = 0.0251 a 0.0565	507	100.0	489	96.4	18	3.6
3 = 0.0566 a 0.1376	507	100.0	468	92.3	39	7.7
4 = 0.1377 a 0.5088	507	100.0	345	68.0	162	32.0
5 = 0.5089 a 0.9947	506	100.0	115	22.7	391	77.3

Cohort of women with invasive cervical cancer registered at INCA and diagnosed between 1999 and 2004.
5 missing.

Table 3
Cox models of survival for patients with invasive cervical cancer

Characteristics	Univariate Cox model		Multivariate Cox model	
	HR	p value	HR_{adj}*	p value
Treatment				
Exclusive radiotherapy	1		1	
Radio + chemotherapy	0.69	<0.001	0.72	<0.001
Quintiles of the propensity score		0.003		0.866

Cohort of women with invasive cervical cancer registered at INCA and diagnosed between 1999 and 2004.

* HR_{adj}=*Hazard Ratio* adjusted for the propensity score.

(38%), gastrointestinal toxicity (22.5%) and abandon of unknown reasons (15.4%). Brachytherapy was applied in 83.3% of patients treated with exclusively RT and 84.1% of patients treated with combined treatment modality.

Patients treated with exclusively radiotherapy received whole pelvic irradiation by anterior–posterior and posterior–anterior parallel ports or a four-field box technique utilizing X-ray energies of 4 MV or greater. Pelvic radiation therapy was administered in 1.7 Gy fractions with a total dose of 51.0 Gy. Intracaviatary brachytherapy was identical to combined modalities.

Survival analysis

Fig. 1 depicts the survival curves for both groups, indicating a statistically significant benefit for the combination of chemo- and radiotherapy (log-rank test— $p<0.001$), with a greater median survival (40.83 vs 28.23 months).

Table 2 shows the proportions of combined treatment according to the quintiles of the propensity score. The scores ranged from 0.0005 to 0.9947, expressing the probability of undergoing chemotherapy.

Based on the hazard ratio constructed from the Cox model, Table 3 shows longer survival for the patients undergoing the combined treatment (HR 0.69 for the combination, $p<0.001$), which did not change on multivariate analysis (HR 0.71).

Finally, Table 4 discloses adjusted mortality rate comparing both groups of treatment. As shown in the table, mortality is statically higher on those who received exclusive radiotherapy (231 *vs* 181/1000 women/year).

Discussion

This study represents the reality of a reference center (INCA) located in a region with a relatively high incidence of invasive cervical cancer [16]. First of all, combined modality treatment for cervical cancer was adopted as the standard treatment at INCA only four years after the NCI alert. This may have resulted from the technical difficulties in adding chemotherapy to routine management of this group of patients. Despite the greater complexity of the procedure, the time between diagnosis and the beginning of treatment became surprisingly shorter in the combination group as compared with that of the group undergoing exclusively radiotherapy. Nevertheless, the median length of time was high for both groups, with only 5.15% of the cases initiating treatment within the first 30 days after diagnosis. It is also important to stress that time from treatment beginning to the end was extremely long in both arms, exceeding 60 days in the great majority.

One must take into account that this was not a randomized study and the potential biases that may have influenced the results (the selection of patients for the groups of treatment and the possible selective losses) should be considered. In addition, it is worth stressing the limitations of our data analysis, which originated from secondary data. Consequently, further information, such as length of time to complete external irradiation, the interval between radiotherapy and the beginning of brachytherapy, the histological subtypes and the associated comorbidities, were not available. As a consequence of long waiting time to begin treatment, it is possible that some cases suffered clinical upstaging, favoring combined modality treatment, but it is not possible to be determined, once staging was done only once. Although educational level may have affected patient selection for treatment scheme in this study and also treatment compliance (higher level in combined modality group), it was not demonstrated on multivariate analysis.

Although the improvement in overall-survival detected in this study could be related to preferential use of the combined treatment for cases with better prognosis, the scarce use of the combination during the first years of the study contrasts with its wide use in the final period, creating a model of the "before and after" type of study. This results in a reduction in the heterogeneity in the clinical condition of both groups of treatment.

The appearance of other concurring modalities, a better supportive structure and evolving differences in the population characteristics could have also influenced the results obtained. Nevertheless, it should be emphasized that the period studied was too short for any significant change in the population (six years). In addition, the structure available for medical care and the supportive measures adopted routinely at the center underwent no changes after 1999. Although brachytherapy technique has been modified in our center since the end of the past decade and the high-dosage therapy with Ir^{192} has

Table 4
Mortality rates between groups of woman with cervical cancer treated with exclusive radiotherapy or combined modality

Treatment	Deaths	Women-year	Rates (CI 95%) per 1000 women-year		Median survival (years)
Exclusive Radiotherapy	1140	4937	231	(218–245)	2.4
Radiotherapy plus Chemotherapy	253	1400	181	(160–204)	3.4
Total	1393	6337	220	(209–232)	2.6

completely replaced the low-dosage brachytherapy since 2001, no study has indicated the superiority of any of these techniques [17,18].

Finally, the results are very similar with those of prospective randomized studies. Confirming the results obtained in other series, the combination of chemotherapy and radiotherapy has also proved beneficial in our cohort, increasing overall survival by 31% (Table 3). Prospective randomized trials conducted by the GOG [6,7,9] showed benefits in overall survival very similar (33 to 40%). Although median survival in both arms seems lower (2.4 years in RT group and 3.4 years in combined modality) compared to GOG studies (4.3 to 4.8 years), one must remember that the cohort was mainly formed by locally advanced tumors (88.7% were stages II or III), whose prognoses are comparatively worse. Besides, extended treatment time in both arms in our cohort probably affected negatively the outcomes. Recently, a Canadian retrospective population-based study has reported comparable results [19].

We conclude that the addition of chemotherapy to RT for cervical cancer resulted in a significant improvement in overall survival at the population level, even considering all the technical difficulties in treating such volume of patients at our center. The magnitude of the observed effect was consistent with the results of the clinical trials that led to the change in clinical practice. Besides, as far as we know, this is the only observational study carried out in a Brazilian center to assess the impact of the association of chemotherapy and radiotherapy on cervical cancer.

Conflict of interest statement
The authors have no conflicts of interest to declare.

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