Californium versus cobalt brachytherapy combined with external-beam radiotherapy for IIB stage cervical cancer: long-term experience of a single institute

Ernestas Janulionis, MD, PhD¹, Prof. Konstantinas Pavilas Valuckas, MD¹, Sarune Liukpetryte, MD¹, Vitalija Samerdokiene, MD², Vydmantas Atkocius, PhD²
¹Radiotherapy and Drug Center, ²Scientific Research Center, National Cancer Institute, Vilnius, Lithuania

Abstract

Purpose: The purpose of this paper was to observe and compare long-term curative effects and complications of FIGO stage IIB cervical cancer patients (n=232) treated with high-dose-rate (HDR) californium (252Cf) neutron or cobalt (60Co) photon intracavitary brachytherapy (ICBT) combined with external-beam radiotherapy (EBRT).

Material and methods: The EBRT dose to the small pelvis was 50 Gy in both groups. The brachytherapy component of 252Cf or 60Co was added in the 3rd week of EBRT, 5 fractions were performed once per week resulting in a total ICBT dose of 40 Gy/Gy eq (point A).

Results: Overall survival (OS) at 5, 10 and 15 years was 63.6%, 50.4% and 38.8% in the 252Cf group and 62.2%, 50.5%, 39.9%, in the 60Co group, respectively (p = 0.74). The percentage of tumour recurrence was statistically significantly lower in the 252Cf group with 7.4 % versus 17.1% in the 60Co group (p = 0.02). Second primary cancers have developed similarly 9.1% and 8.1% cases for 252Cf and 60Co groups, respectively.

Conclusions: Our long-term retrospective study comparing 252Cf and 60Co isotopes with brachytherapy in combined treatment of FIGO IIB stage cervix carcinoma patients shows, that overall survival in the both groups are similar. However, the recurrence of tumour was significantly lower in the 252Cf group. The incidence of second primary cancers was similar in both groups.

Key words: brachytherapy, 252Cf, cervical cancer, 60Co, neutron brachytherapy.

Purpose

Cervical cancer is still the leading cause of cancer deaths in women. Among women, it is the fourth leading cause of cancer worldwide by incidence and mortality in 2012. In Lithuania, its incidence is ranked in third place, and its mortality in sixth place [1].

A combination of intracavitary brachytherapy (ICBT) with external beam radiotherapy (EBRT) is used to treat advanced cervical cancer. Gamma radioactive nuclides such as 60Co, 137Cs, and 192Ir are commonly used in brachytherapy to treat cervical cancer patients.

Gamma rays provide low linear energy transfer radiation. 252Cf as a neutron emitting radioactive isotope, produces high linear energy transfer (high-LET) radiation. High-LET radiation provides several radiobiological benefits: a relatively high biological effectiveness value (RBE), inhibition of cell damage repair, lower dependence of radiation sensitivity on the cell cycle, as well as a low oxygen enhancement ratio [2]. These advantages of high-LET radiotherapy are most pronounced in the treatment of locally advanced tumors containing high proportions of hypoxic cells; in slowly growing tumors containing high proportions of cells that are in the radio resistant phases, as well as in tumors proliferating too fast to benefit from the conventional 6-week 30-fraction scheme [3].

In this paper, we retrospectively analyzed long-term data of 232 FIGO stage IIB patients treated from 1989 to 1999 with 252Cf or 60Co ICBT combined with EBRT at the National Cancer Institute, Vilnius, Lithuania. Our purpose was to observe and compare the long-term curative effects and complications.

Material and methods

Patient population

From 1989 to 1999, 232 stage IIB previously untreated patients with biopsy-proven cervical cancer were treated with HDR 252Cf or 60Co ICBT and EBRT at the National Cancer Institute, Vilnius: 121 patients were treated with neutron brachytherapy by 252Cf, and 111 with 60Co ICBT.
From October 1996 till April 1998, all patients were treated with neutron brachytherapy by 252Cf combined with EBRT. The stage of disease was determined according to the FIGO classification on the basis of the following examinations: inspection, palpation, biopsy, cystoscopy, pyelography, abdominal ultrasonography, chest X-ray, and hematologic/biochemical tests of the blood. Patient characteristics are listed in Table 1. Eligibility criteria included histologically confirmed diagnosis. Information about radiotherapy was derived from hospital registry records and follow-up data records. The following data were also collected: age at initial diagnosis, pathological report, late radiation complications, hemoglobin level, body mass index, concurrent disease. During the follow-up period, the vital status of the subjects were determined using resident registration records available from the Death and Population Registers in our country, and causes of death were confirmed by the death certificate from the Archives Department under the government of the Lithuania.

The protocol for this study was approved by the Regional Biomedical Research Ethical Committee in Vilnius (No 158200-13-619-199, 2013-06-11).

Treatment

For both groups, EBRT was delivered by the 60Co units AGAT-B and Rokuks-M. The EBRT dose was delivered to the small pelvis through anteroposterior and posteroanterior portals 15-18 by 15-19 cm at the skin surface. The applied total dose of 50 Gy (1.8-2.0 Gy per fraction) was divided to 16-18 Gy by full field, and the residual dose by split fields to the small pelvis. The central shielding of the split field was 4 cm in width and was applied in the third treatment week of EBRT after the 16-18 Gy.

The brachytherapy component of 252Cf or 60Co was added in the 3rd week of EBRT. Intracavitary brachytherapy was administered once per week with a fraction dose of 8.0 Gy/Gy(eq) (point A), and 5 fractions were performed resulting in a total ICBT dose of 40 Gy/Gy(eq).

A USSR after loader (ANET-V) was used with three 252Cf sources, which had an active length of 1.5 x 9.0 mm: two static dwell positions at the lateral positions and one at the central applicator moving according proposed dwell time program (step 1 cm). The 252Cf source activities at the start was 1410.2 µg for the central source and 360.4 µg each for the lateral sources; and at the end of project 125.5 µg and 32.1 µg, respectively. Irradiation time was in the interval from 10 minutes at the start to 100 minutes at the end of the project. The ICBT 252Cf treatment irradiation dose-planning was performed by COSPO program (Russia) based on the Rjabukin [4] formula. The reference point was point A. The treatment characteristics are shown in Table 2.

Follow ups were performed for each patient every 3 months in the first year after treatment and every 6 months thereafter.

Statistical analysis

Proportions were compared using the χ² or Fisher test. The Kaplan-Meier method was used to estimate overall survival (OS) and disease-free survival (DFS). Differences between groups were calculated using the log-rank test. Univariate and multivariate Cox regression was performed to assess risk factors associated with mortality. P-value < 0.05 was considered statistically significant. Analysis was performed using SPSS 21 software.

Results

The median follow-up for 252Cf and 60Co treated patients was 124.1 (interquartile range [IQR]: 24.9-206.5) and 118.3 (IQR: 34.4-177.4) months, respectively. The median age was 54 (IQR: 42-65) years in the 252Cf group and 50 (IQR: 42-61) years in the 60Co group.

The survival rates were calculated from the first treatment date to the last follow-up examination. The survival rates are shown in Figures 1 and 2. Overall survival at 5,
10, and 15 years was 63.6%, 50.4% and 38.8% in the 252 Cf group, and 62.2%, 50.5%, 39.9% in the 60 Co group, respectively ($p = 0.74$).

In the 252 Cf group, the percentage of tumour recurrence was statistically significant lower than in the 60 Co group ($p = 0.02$). Also the percentage of distant metastases was lower in the 252 Cf group than in the 60 Co group ($p = 0.28$). The relapse pattern in both groups is given in Table 3.

Radiation related complications are shown in Table 4. The adverse effects and radiation complications (cystitis, proctitis II-III grade according to RTOG/EORTC scoring and hydronephrosis) were similar in both groups ranging from 1.6% to 13.5%.

During follow up, the percentage of a second primary cancer in the 252 Cf group was similar to the 60 Co group: 9.1% versus 8.1%, respectively ($p = 0.79$).

The results of univariate analysis showed that the histopathologic grade, recurrence, concurrent disease, hemoglobin level, and body mass index were factors that statistically significantly influenced patient prognosis in the 252 Cf group ($p < 0.05$); and histopathology, recurrence and metastases were factors that influenced statistically significantly patient prognosis in the 60 Co group ($p < 0.05$). However, the Cox multiple regression analysis showed that just a histopathologic grade was an independently significant prognostic factor in the 252 Cf group, and for recurrence in the 60 Co group.

Discussion

Since the early 1970s, cervical cancer has been recognized as an ideal condition for the use of 252 Cf [3]. Several researchers published their experience using 252 Cf in cervical cancer treatment with favorable results [5, 6, 7, 8, 9]. However, to our knowledge, this is the first study, which has revealed the results of curative effects and complications for a period of 20 years for IIB FIGO stage cervical cancer patients treated with 252 Cf neutron or 60 Co gamma intracavitary brachytherapy combined with external photon beam radiotherapy.
The majority of the clinical studies were based on Maruyama’s empirical findings in an early application of the $^{252}$Cf source in the initial phase of radiotherapy. Maruyama et al. analyzed 41 cases of cervical carcinoma at stage IIB. Patients that received application of the $^{252}$Cf implants in the delayed phase of radiotherapy had a significantly greater rate (40% vs. 3%) for developing severe complications (pelvic necrosis, fistulas). Neutron brachytherapy caused tumors to regress rapidly and completely, which allowed the neutron dose to adjacent radiosensitive organs (bladder, rectum, sigmoid colon, and bowel) to become excessive. The delayed $^{252}$Cf implant apparently contributed to the greater risk for normal tissue complications [9]. Despite the fact that in our study high-dose rate brachytherapy component of $^{252}$Cf was added in the 3rd week of EBRT and administered once per week with a fraction dose of 8.0 Gy/Gy$_{eq}$ (point A), 5 fractions, our observed-results of radiation complications in $^{252}$Cf group are similar comparing with other researchers. Xin Lei et al. also used the HDR brachytherapy component of $^{252}$Cf and reported incidence rates of late complications 7.1%, 6.2%, 4.9% in the rectum, bladder, and small bowel, respectively [7]. Worse results were reported by Ferrigno et al.: the 5-year incidence rates of late complications in the rectum, bladder, and small bowel were 16.0%, 11.0%, and 14.0%, respectively in patients treated with high-dose-rate $^{192}$Ir ICBT [10]. In the Zhao et al. study, early radiation complications such as radiation proctitis (7.8%) and radiation cystitis (4.7%), and late radiation complication – protracted radiation proctitis – with an incidence of 5.5% were observed in patients treated with high-dose-rate $^{252}$Cf ICBT [6]. Tacev et al. published a randomized study showing that treatment of cervical carcinoma with low-dose-rate $^{252}$Cf neutron intraluminal brachytherapy resulted in radiation cystitis, radiation proctitis, and rectal ulcer rates of 16.2%, 18.0% and 0.8%, respectively [8].

### Table 3. Relapse pattern of IIB FIGO stage cervical cancer patients

| Characteristics | EBRT and $^{252}$Cf-ICBT | EBRT and $^{60}$Co-ICBT | p-value |
|-----------------|--------------------------|-------------------------|---------|
|                 | Patients | %   | Patients | %   |         |
| Recurrence      |           |     |           |     |         |
| No              | 112      | 92.6 | 92       | 82.9 |         |
| Yes             | 9        | 7.4  | 19       | 17.1 | 0.02    |
| Metastases      |           |     |           |     |         |
| No              | 111      | 91.7 | 97       | 87.4 |         |
| Yes             | 10       | 8.3  | 14       | 12.6 | 0.28    |

EBRT = external-beam radiotherapy, $^{252}$Cf = californium-252, ICBT = intracavitary brachytherapy, $^{60}$Co = cobalt-60

### Table 4. Radiation complications of IIB FIGO stage cervical cancer patients

| Complications | EBRT and $^{252}$Cf-ICBT | EBRT and $^{60}$Co-ICBT | p-value |
|---------------|--------------------------|-------------------------|---------|
|               | Patients | %   | Patients | %   |         |
| Adverse effects |         |     |           |     |         |
| No            | 108      | 89.3 | 96       | 86.5 | 0.52    |
| Yes           | 13       | 10.7 | 15       | 13.5 |         |
| Cystitis      |           |     |           |     |         |
| No            | 112      | 92.6 | 103      | 92.8 | 0.95    |
| Yes           | 9        | 7.4  | 8        | 7.2  |         |
| Proctitis     |           |     |           |     |         |
| No            | 119      | 98.4 | 108      | 97.3 | 0.58    |
| Yes           | 2        | 1.6  | 3        | 2.7  |         |
| Hydronephrosis |         |     |           |     |         |
| No            | 118      | 97.5 | 105      | 94.6 | 0.25    |
| Yes           | 3        | 2.5  | 6        | 5.4  |         |

EBRT = external-beam radiotherapy, $^{252}$Cf = californium-252, ICBT = intracavitary brachytherapy, $^{60}$Co = cobalt-60
Considering all this data, the incidence of late radiation proctitis (1.7%) was lower and the incidence of late radiation cystitis (7.4%) was similar within our study in the 252Cf group.

After the treatment, we observed a statistically significant \( p = 0.02 \) lower recurrence rate in the 252Cf group (252Cf group - 7.4% vs. 17.1% 60Co group). The rate of metastases was also lower in the 252Cf group (252Cf group - 8.3% vs. 12.6% 60Co group), but statistically not significant \( p = 0.28 \). A randomized phase III trial conducted by Tacev et al., also reported a smaller recurrence rate in the small pelvis in IIB stage cervical cancer patients treated with 252Cf, than only treated with gamma irradiation: 7.3% vs. 16.0%, respectively but not statistically significant. The appearance of distant metastases also was lower in the 252Cf group (252Cf group – 5.4% vs. 12.0% gamma radiation group). It’s important to emphasize that in the Tacev et al. trial, the 252Cf sources were a low dose rate, and the irradiation time lasted several days. This means that the radiobiological 252Cf irradiation was very different in comparison with the HDR 252Cf irradiation [8]. Maruyama et al. also showed a similar recurrence rate (6.0%) in II stage (IIA and IIB stages) cervical cancer patients treated with 252Cf but the rate of metastases (15.0%) was higher than in our study [5].

The study comparing the 252Cf brachytherapy component and conventional gamma radiation conducted by Tacev et al., showed better OS rates: the overall 5-year survival rate for IIB was better by 13.4% for 252Cf patients than for patients receiving conventional treatment (85.4% vs. 72.0%, respectively). However, we cannot omit the fact that they used low-dose rate brachytherapy [8]. Another report dealing with long-term results with HDR 252Cf treatment combined with EBRT in cervical cancer was published in China by Lei et al., and it showed the overall survival rate for IIB stage at 5 and 5 years was 76.2% and 66.1%, respectively [7]. Maruyama et al., in whose study the 252Cf neutron brachytherapy was combined with surgery and EBRT, showed similar results to our long-term results. The survival rates for stage II (IIA and IIB) were 62.0% at 5 years and 61.0% at 10 years [5]. The 10 years OS results in our study maybe were lower because of the fact that we did not have a surgery component in our study and we analyzed just the IIB stage. However, there is no data for a period of 20 years OS in order to make a comparison.

The risk of developing a second primary cancer after radiotherapy becomes more significant because of the improvement in long-term survival. Xin Lei, in his study, detected just 1.6% second primary cancers in patients treated with HDR 252Cf brachytherapy. However, the median of the follow up in the Xin Lei study was short – just 44 months [7]. The other study comparing breast cancer patients undergoing hypofractionated EBRT and brachytherapy by 252Cf sources, with those irradiated by giving conventional EBRT, conducted by Valuckas et al., showed a similar rate of second primary cancers among the groups: conventional radiotherapy – 18.0% and hypofractionated radiotherapy + postoperative brachytherapy by 252Cf sources – 18.8% [11]. During our long follow-up, the rate of second primary cancer between the groups was similar. The deep analysis of a second primary cancer after radiotherapy including HDR 252Cf brachytherapy for cervical cancer was published by Samerdokiene et al., this study shows no significant difference in rates or distribution of second primary cancer in women treated with neutron brachytherapy compared with photon brachytherapy [12]. During our long follow-up, the rate of second primary cancer between the groups was similar: 9.1% and 8.1% cases for 252Cf and 60Co groups, respectively.

Conclusions

Due to the Rjabukhin [4] formulae of an equivalent dose calculation and fractionation that was used, our results show similar survival results for 252Cf and 60Co brachytherapy in the treatment of FIGO IIB stage cervix carcinoma patients. The number of tumor recurrences was significant lower in the 252Cf group. The amount of second primary cancers was similar in both groups.

Acknowledgements

This research was funded by a grant (No MIP-036/ 2013) of the Research Council of Lithuania. Authors expresses sincere thanks for the statistical calculations to T. Rakovskaja as well to G. Kovács for manuscript editing advice, and to G.P. Elisyutin for excellent technological status of neutron afterloader ANET-V maintained all ten years.

Disclosure

Authors report no conflict of interest.

References

1. Ferlay J, Soerjomataram I, Ervik M et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11. Lyon, France: International Agency for Research on Cancer; 2013. Available from; http://globocan.iarc.fr, accessed on 24/08/2014.

2. Nuclear data for neutron therapy: Status and future needs. IAEA-TECDOC-992, 1997.

3. Zhang M, Xu H, Pan S et al. Low-dose-rate californium-252 neutron intracavitary afterloading radiotherapy combined with conformal radiotherapy for treatment of cervical cancer. Int J Radiat Oncol Biol Phys 2012; 83: 966-971.

4. Rjabukhin YS. Relative biological efficiency of Cf-252 sources. Med Radiol 1985; 30: 53-59 [in Russian].

5. Maruyama Y, van Nagell JR, Yoneda J et al. A review of californium-252 neutron brachytherapy for cervical cancer. Cancer 1991; 68: 1189-1197.

6. Zhao H, Wang K, Sun J et al. Clinical report on external irradiation combined with californium-252 neutron intraluminal brachytherapy for cervical carcinoma treatment. Tumori 2007; 93: 636-640.

7. Lei X, Qian CY, Qing Y et al. Californium-252 brachytherapy combined with external-beam radiotherapy for cervical cancer: long-term treatment results. Int J Radiat Oncol Biol Phys 2011; 81: 1264-1270.

8. Tacev T, Ptácková B, Strnad V. Californium-252 (252Cf) versus conventional gamma radiation in the brachytherapy of advanced cervical carcinoma long-term treatment results of a randomized study. Strahlenther Onkol 2003; 179: 377-384.
9. Maruyama Y, van Nagell JR, Yoneda J et al. Schedule in Cf-252 neutron brachytherapy: complications after delayed implant therapy for cervical cancer in a phase II trial. *Am J Clin Oncol* 1993; 16: 168-174.

10. Ferrigno R, dos Santos Novaes PE, Pellizzon AC et al. High dose-rate brachytherapy in the treatment of uterine cervix cancer. Analysis of dose effectiveness and late complications. *Int J Radiat Oncol Biol Phys* 2001; 50: 1123-1135.

11. Valuckas KP, Atkocius V, Kuzmickiene I et al. Second malignancies following conventional or combined 252Cf neutron brachytherapy with external beam radiotherapy for breast cancer. *J Radiat Res* 2013; 54: 872-879.

12. Samerdokiene V, Valuckas KP, Janulionis E et al. Second primary malignancies after radiotherapy including HDR 252Cf brachytherapy for cervical cancer. Brachytherapy; Available from: http://dx.doi.org/10.1016/j.brachy.2015.06.006, accessed on 12/08/2015.