Original Article

Outcome of Carcinoma Cervix Uteri Patients of Older Than 60 Years versus Less Than 60 Year

Kesarwani Radha*, Prakash Gyan**, Maurya Anil K.***, Singh Virendra****

*Assistant Professor
***Lecturer ****Professor,
Radiotherapy Department,
**Assistant Professor
(Statistics), Department of
Community Medicine,
Moti Lal Nehru Medical
College, Allahabad, Uttar
Pradesh 211002, India.

Corresponding Author:
Anil Kumar Maurya,
Lecturer, Radiotherapy
Department, Moti Lal
Nehru Medical College,
Allahabad, Uttar Pradesh
211002, India.
E-mail:
maurya.anilkumar38@gmail.com

Abstract

Aims and Objectives: Elderly patients of carcinoma cervix uteri are increasing in number. Outcome of cervical cancer with relation to age is controversial. We conducted a retrospective analysis in treated patients of carcinoma cervix uteri to investigate characteristics and outcome of patients older than 60 years in comparison to patients younger than 60 years. *Materials and Methods*: Medical records of 92 patients of carcinoma cervix uteri who had been treated with radiotherapy or radiotherapy combined with chemotherapy from May'2013 to December'2015 were retrospectively analyzed. The patients were divided in to the two age groups: Group I patients older than 60 years and in group II patients younger than 60 years, there were 37 patients in group I and 55 patients in group II. Patient characteristics, treatment and toxicities were evaluated. *Results*: With a median follow-up time of 28 months (range 4-49 months), disease free survival was 51.35% and 40% in group I and II respectively (p value- 0.565) whereas overall survival was 62.16% and 45.45% in two groups respectively (p value- 0.414), hence DFS and OS are not statistically significant. However in incidence of anemia and neutropenia there was statistically significant difference between the two groups (p value 0.0222, 0.0096 for anemia and neutropenia respectively).

Conclusions: There is no statistically significant difference in outcome of cervical cancer patients older and younger than 60 years is in our study with respect to DFS and OS. Haematological toxicities were found more in patients more than 60 years in comparison to patients younger than 60 years.

Keywords: Cervical Cancer; Women Older than 60 Years; Haematological Toxicity.

Introduction

Cervical cancer is the most frequent gynaecological cancer worldwide and the second common cancer in females in India [1-3], it is the commonest cause of cancer death in women in developing countries, [2] where almost half of the patients are diagnosed with locally advanced disease. [3] Cervical cancer is the second leading cause of the female cancer deaths in India [3]. The peak age of incidence of cervical cancer is 55–59 years [4].

However, the impact of age on survival of patients with cervical cancer remains uncertain. Some older studies suggested that cervical cancer has the same prognosis in old and young women [5]. Others suggested that younger age is an unfavorable prognostic factor, especially in more advanced stages [6]. In contrast, Wright et al demonstrated that age is a poor prognostic factor for cervical cancer [7]. Moreover, it has been shown that younger patients may have improved outcome compared to older patients [8–10] and that advanced age is linked to decreased survival in a variety of cancers [11-12].

Since the outcome of cervical cancer related to age is controversial, and the

determination of the effect of age on outcome is complicated by several related issues, including the risk of death from competing age-related illnesses, stage of disease, method of treatment, and histologic type, [13-14] we conducted a retrospective analysis in patients treated in our institution and associated hospital in order to investigate the outcome, patient characteristics, treatment, and toxicities of older patients with carcinoma of the uterine cervix.

Materials and Methods

Patients

The study was conducted in the Department of Radiotherapy of the Moti Lal Nehru Medical College and associated hospitals, Allahabad. Data were collected retrospectively from the records of 92 consecutive patients with cervical cancer who had been treated with radiotherapy or combined radiotherapy and chemotherapy from May 2013 to December 2015 and fulfilling the following inclusion criteria were included for this study: histological diagnosis of primary cervical cancer, both early and locally advanced stage, completion of radical radiotherapy, or radical radiotherapy with concurrent chemotherapy and completion of at least three months of follow up after treatment or event occurred before that period. All patients had provided written informed consent for treatment.

The patients included in this study presented with International Federation of Gynecology and Obstetrics (FIGO) stages I–IV, good performance status (Eastern Cooperative Oncology Group 0 [asymptomatic], or 1 [symptomatic but ambulatory]), 2[Unable to carry normal activity or to do active work], no uncontrolled concomitant disease, no connective tissue disease, and no prior irradiation. For evaluation, we divided our cohort into two age-groups: Group I- patients ≥ 60 years old, and Group II- patients <60 years old. There were 37 women in group I, 55 in group II.

External beam radiation therapy (EBRT) was delivered in a conventional fraction (2 Gy/fraction, five fractions/week) using a 6 MV photon beam and sometimes 15 MV photon beam whenever indicated from a dual energy linear accelerator. A total dose of 50 Gy was administered to the entire pelvis with a 4-field box technique. Two weeks after completion of EBRT, two intracavitary brachytherapy applications were done at a dose of 7 Gy each. The dose was prescribed to ICRU-38 point A, which was delivered by a remote afterloading high dose rate brachytherapy machine with Ir-192 source. External beam radiation therapy

was interrupted if the white blood cell count fell below 4,000/mm^3 or if platelets fell below 1,00,000/mm^3 and was resumed once counts rose above these levels.

Cisplatin chemotherapy was given in a dose of 40 mg/m^2 maximum total dose 50 mg weekly during radiotherapy from the first day with radiotherapy. Patients were seen weekly by a physician for a physical examination and a complete blood count test. Chemotherapy was interrupted if patients had the total white blood cell count was <4,000/mm^3, or platelets were <100,000/mm^3.

Toxicity

During treatment, toxicities were assessed weekly and graded in accordance with the National Cancer Institute Common Terminology Criteria of Adverse Events: 1-mild; 2-moderate; 3- severe; and 4- life-threatening or disabling [15].

Statistical Analyses

The data were collected and information were analysed with the IBM SPSS 20.0 and Microsoft Excel 2016. The results are considered significant at 5% level of significance under two-tailed test.

Results

Patient Characteristics

In total, 92 patients were included from May 2013 to December 2015. The median age of the patients at the time of diagnosis was 60.0 years [In group I 66 years (standard deviation 5.06) and in group II 55 years (standard deviation 6.28)] (range 33–75 years). Eighty eight patients had squamous cell carcinoma , four had adenosquamous carcinoma. Two patients were diagnosed in stage IB (in group II), forty six patients were diagnosed in FIGO stage II (21 in group I, 25 in group II) and 44 patients were diagnosed in FIGO stage III (16 in group I, 28 in group II). Of the 92 patients analyzed, 8 patients (8/37) in group I received concurrent chemotherapy. Seventeen (17/55) in group II completed that treatment.

During the follow-up interval, seven patients in group I and ten patients in group II died. All patients died of tumour-related disease. Tumour recurrence was observed in 18 patients (seven in group I, 11 in group II). In the entire group, metastasis occurred in seven patients (zero in group I, seven in group II). Patient characteristics are outlined in Table 1.

Survival and Local Control

With a median follow-up time of 28 months (range 4–49 months), Disease-free survival for the both groups was 51.35% and 40% (p value- 0.565) whereas the overall survival was 62.16% and 45.45% (p value- 0.414). Hence, the DFS & OS are not statistically significant. [Figure 1A and 1B and Table 2].

Toxicities

Anaemia and neutropenia were found in 39 and 24 patients, respectively. In group I, 21 and 15 patients developed anemia and neutropenia, while in group II, 18 and 9 patients developed these side effects. The differences in acute hematologic toxicity between the two patient groups was significant ($P = 0.0222$ for anemia, $P = 0.0096$ for neutropenia) (Table 3). More cases of hematologic toxicity occured in group I than in group II. In Group I anaemia, neutropenia and thrombocytopenia incidences were 44.83%, 31.03% and 6.90% respectively in RT group while in CT-RT group those incidences were 100.0%, 75.0% and 37.5% respectively while for the group II anaemia, neutropenia and thrombocytopenia incidences were 21.05%, 10.53% and 2.63% respectively in RT group while in CT-RT group those incidences were 58.82%, 29.41% and 5.88% respectively (Table 4). Seven patients developed thrombocytopenia. The incidence of this was 13.5% and 3.6% in groups I and II,

Table 1: Characteristics of patients

Particulars	Group I[a]	%	Group II[b]	%	P-value
Hemoglobin Level					
>= 10g/dL	24	43.24	39	67.27	0.64
< 10g/dL	13	56.76	16	32.73	
ECOG Performance Status					
0 Or 1	32	86.49	49	89.09	0.705
>1	5	13.51	6	10.91	
Stage					
IB	0	0	2	3.64	0.2401
IIA	2	56.76	0	45.45	0.2878
IIB	19		25		
III	16	43.24	28	50.91	0.4708
Grade of tumour					
1 – 2	20	54.05	29	52.73	0.92
3 – 4	17	45.95	26	47.27	
Initial Treatment					
R	29	78.38	38	69.09	0.3272
R+C	08	21.62	17	30.91	
Relapse	07	18.92	11	20.00	0.8875
Metastasis	00	00.00	07	12.73	0.0239

Notes- [a]Patients ≥ 60 years old, n=37, [b]Patients d"60 years old, n=55
R= Radiotherapy, R+C= Radiotherapy + Chemotherapy

Table 2: Two year disease free survival, overall survival stratified by patient group

	Group I[a] (%)	Group II[b] (%)	P value
Disease free survival rates	51.35	40	0.565
Overall survival	62.16	45.45	0.414

Notes- [a]Patients ≥ 60 years old, n=37, [b]Patients d"60 years old, n=55

Table 3: Toxicities stratified by patients group

	Group I[a]	%	Group II[b]	%	p-value
Anemia	21	35.14	18	32.73	0.0222
Neutropenia	15	40.54	9	16.36	0.0096
Thrombocytopenia	5	13.51	2	3.64	0.0797
Subcutaneous tissue	10	27.03	22	40.0	0.2003
Gastrointestinal	4	10.81	9	16.36	0.4543
Genitourinary	3	8.11	6	10.91	0.6547

Notes- [a]Patients ≥ 60 years old, n=37, [b]Patients d"60 years old, n=55

Table 4: Haematological Toxicity in both groups as per treatment

Toxicity	Group I[a]		Group II[b]		
	RT		RT		
	Number	%	Number	%	
Anemia	13/29	44.83	8/38	21.05	0.0377
Neutropenia	9/29	31.03	4/38	10.53	0.0355
Thrombocytopenia	2/29	6.90	1/38	2.63	0.4028
	CT-RT		CT-RT		
	Number	%	Number	%	
Anemia	8/8	100.0	10/17	58.82	0.0323
Neutropenia	6/8	75.0	5/17	29.41	0.0322
Thrombocytopenia	3/8	37.5	1/17	5.88	0.0442

Notes- [a]Patients $\geq$ 60 years old, n=37, [b]Patients $\leq$ 60 years old, n=55
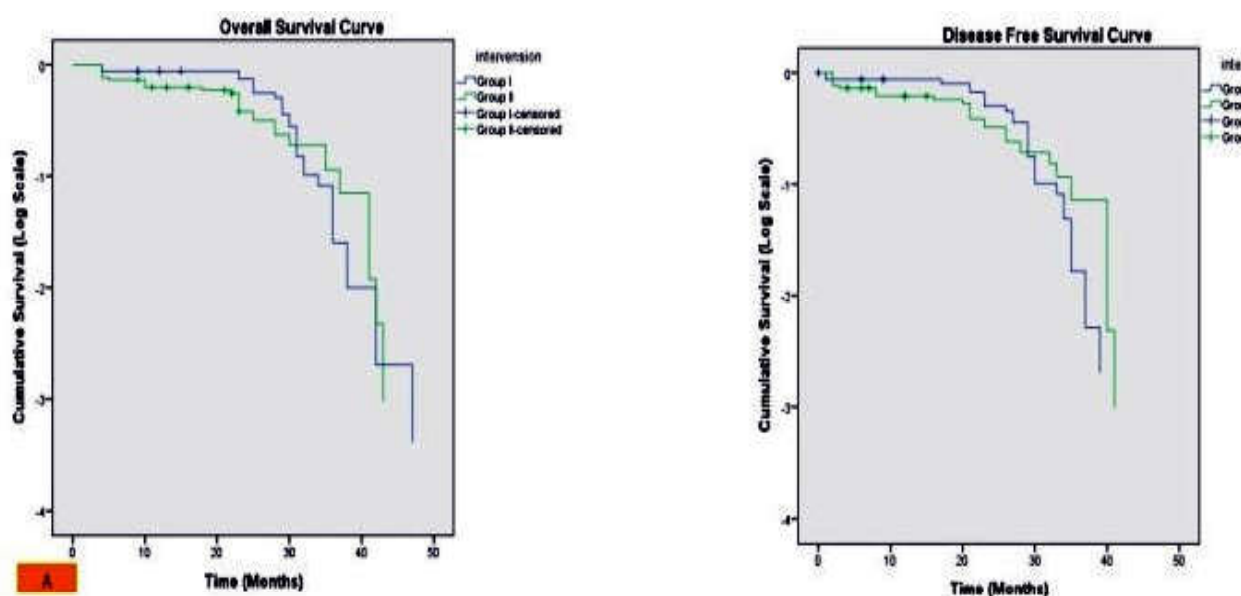

Fig. 1 (A and B): Survival analysis in cervical carcinoma, stratified by groups I and II **(A)** Overall survival curves. **(B)** Disease-free survival curves

respectively, the difference is not significant (P= 0.0797). There was no statistical significant difference between the patient groups in terms of the incidence of subcutaneous, gastrointestinal, or genitourinary toxicities (Table 3).

Discussion

Uterine cervix cancer is mainly a disease of middle-aged and older women [16-17]. Various studies have demonstrated that presentation of older women with more advanced-stage disease at the time of diagnosis. As per study by Brun et al older women present with more advanced disease in France [18]. Similarly, Ioka et al reported that in Japan older women present with a later stage at diagnosis and have a poorer outcome,

likely from underutilization of Pap smears [19]. We found that majority of patients of older than 60 years of age in our study had advanced-stage disease (94.59%) at presentation. In our study percentage of patients with advanced-stage cervical cancer appears to be significantly higher than the advanced disease percentage of patients found in large population studies.

Although large population-based studies have also demonstrated that survival for cervical cancer is inversely correlated with stage, survival among older women regardless of stage has been reported to be worse than women in their 40s and 50s [18]. But in our study, there was no statistically significant difference between the two groups in disease-free survival and overall survival in spite of patients older than 60 years being treated less aggressively than

patients younger than 60 years of age. This is in accordance with Lindegaard et al [20] and Ying Gao et al. [21] Lindegaard et al [20] found that age was not a significant variable in any of the investigated end points when standard treatment protocols were completed by reviewing radiotherapy treatment in 114 women with a median age of 75.5 years. Our data support the view that outcomes in women older than 60 years not be independently correlated with age alone. In retrospectively study with large population, the survival of elderly patients was always poorer than younger patients [22-24].

For the elderly, hematopoietic and immune systems functional deficiencies present in the aging process seems to have little physiological importance in healthy individuals. In such cases, changes in these systems, including decrease in hemoglobin concentration, decrease in bone marrow cellularity and functionality, decreased polymorphonuclear function, lymphocytes and monocytes (with concomitant deficiency of cell-mediated immunity) [25-26] do not seem to have a great impact on the quality of life of physically healthy individuals, although it is known that there are impacts regarding anemia detectable by laboratory tests, capacity of bone marrow to respond to more intensive demands and greater susceptibility of the elderly patient to infections [27].

Pelvic radiotherapy contributes significantly to the development of haematological toxicity. More than one-half of the body's bone marrow (BM) is located in the os coxae, sacrum, proximal femora, and lower lumbar spine [28], these areas are included in the treatment volume with conventional pelvic RT. Bone marrow activity declines after RT, [22] and BM regeneration varies with radiation doses used clinically [29-33].

For the elderly patient with indication for radiation treatment, one must bear in mind that there is always the possibility that such patient may have already been submitted to other treatment modalities with prospects of severe myelotoxicity, such as chemotherapy that implies, for example, symptomatic anemia, pancytopenia and risk for infections, with progression to sepsis and death. In the irradiation of bone marrow compartment (for example, bones of the axial spine and hip), the recovery of peripheral blood cell count occurs more rapidly than bone marrow regeneration by the compensatory effect of the non-irradiated bone marrow; and, additionally to age, the recovery of the irradiated bone marrow is influenced by associated chemotherapy, dose and irradiated volume and survival after irradiation [34].

Specifically as regards anaemia, there are indications that lower haemoglobin levels may be associated with worse treatment outcomes, for certain neoplasms, and in such cases specific therapeutic approaches should be considered [35].

In a study by Wang et al [36] in elderly patients of carcinoma cervix, 31.5% experienced Grade 3 or higher acute hematological toxicity, the incidences in patients treated with RT and CCRT were 16.3% and 62.5%, respectively (p < 0.001). In our study among elderly patients anaemia, neutropenia and thrombocytopenia incidences were 44.83%, 31.03% and 6.90% respectively in RT group while in CT-RT group those incidences were 100.0%, 75.0% and 37.5% respectively (Table 4). The differences in acute hematologic toxicity between the two patient groups >60 years and <60 years was significant ($P = 0.0222$ for anemia, $P = 0.0096$ for neutropenia) while the incidence of thrombocytopenia was 13.5% and 3.6% in two groups respectively, the difference is not significant (P= 0.0797).

Conclusions

Age may not be an independent prognostic factor with respect to response and survival as there is no statistically significant difference in disease free and overall survival in our study, however haematological toxicity are significantly raised with and without chemotherapy with increasing age especially with respect to anaemia and neutropenia.The present study explores the important role of age is on haematological toxicity for anemia , neutropenia and on the other hand thrombocytopenia incidence is not significant.

References

1. Denny L. Cervical cancer: prevention and treatment. Discover Med. 2012;14:125-31.

2. Petersson F. Carcinoma of the cervix. In annual report on the results of treatments in gynaecological cancer. Stockholm, Sweden: International Federation of Gynecology and Obstetrics, 1998.p.29-33.

3. ICO Information Centre on HPV and cancer. Human Papillomavirus and Related Diseases in India (Summary Report 2017-04-19);2017.

4. Aswathy Sreedevi, Reshma Javed and Avani Dinesh. Epidemiology of cervical cancer with special focus on India. Int J Womens Health 2015;7:405–414.

5. Goff BA, Muntz HG, Paley PJ, Tamimi HK, Koh WJ, Greer BE. Impact of surgical staging in women with locally advanced cervical cancer. Gynecol Oncol. 1999;74(3):436–442.

6. Takeda N, Sakuragi N, Takeda M, et al. Multivariate analysis of histopathologic prognostic factors for invasive cervical cancer treated with radical hysterectomy and systematic retroperitoneal lymphadenectomy. Acta Obstet Gynecol Scand. 2002;81(12):1144–1151.

7. Hertel H, Köhler C, Elhawary T, Michels W, Possover M, Schneider A. Laparoscopic staging compared with imaging techniques in the staging of advanced cervical cancer. Gynecol Oncol. 2002;87(1):46-51.

8. Marnitz S, Köhler C, Roth C, Füller J, Hinkelbein W, Schneider A. Is there a benefit of a pretreatment laparoscopic transperitoneal surgical staging in patients with advanced cervical cancer? Gynecol Oncol. 2005;99(3):536–544.

9. Sakuragi N, Satoh C, Takeda N, et al. Incidence and distribution pattern of pelvic and paraaortic lymph node metastasis in patients with stage IB, IIA, IIB cervical carcinoma treated with radical hysterectomy. Cancer. 1999;85(7):1547–1554.

10. PE Castle, J Jeronimo, M Schiffman, et al. Age-related changes of the cervix influence human papilloma-virus type distribution. Cancer Res. 2006;66(2): 1218–1224.

11. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. N Engl J Med. 1998;338(7): 423–428.

12. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189(1): 12–19.

13. Gillison ML, Shah KV. Chapter 9: Role of mucosal human papillo-mavirus in nongenital cancers. J Natl Cancer Inst Monogr. 2003;(31):57–65.

14. Chuang LC, Chen HC, You SL, et al. Association between human papil-lomavirus and adeno-carcinoma of rectum and recto-sigmoid junction: a cohort study of 10,612 women in Taiwan. Cancer Causes Control. 2010;21(12):2123–2128.

15. Trotti A, Colevas D, Setser A, Rusch V, Jaques D, Budach V et al. CTCAE vs 3.0: Development of a Comprehensive Grading System for the Adverse Effects of Cancer Treatment. Semins in Rad Oncol 2003;13:76-81.

16. Bulk S, Visser O, Rozendaal L, Verheijen RH, Meijer CJ. Cervical cancer in the Netherlands 1989–1998: decrease of squamous cell carcinoma in older women, increase of adenocarcinoma in younger women. Int J Cancer 2005;113(6):1005–1009.

17. Kastritis E, Bamias A, Bozas G, et al. The impact of age in the outcome of patients with advanced or recurrent cervical cancer after platinum-based chemotherapy. Gynecol Oncol 2007;104(2):372–376.

18. Brun JL, Stoven-Camou D, Trouette R, Lopez M, Chene G, Hocké C. Survival and prognosis of women with invasive cervical cancer according to age. Gynecol Oncol 2003;91(2):395–401.

19. A Ioka, H Tsukuma, W Ajiki, et al. Influence of age on cervical cancer survival in Japan. Jpn J Clin Oncol 2005;35(8):464–469.

20. Lindegaard JC, Thranov IR, Engelholm SA. Radiotherapy in the management of cervical cancer in elderly patients. Radiother Oncol 2000;56(1):9-15.

21. Ying Gao, Jin-lu Ma, Fei Gao, Li-ping Song. The evaluation of older patients with cervical cancer. Clinical Interventions in Aging 2013;8:783–788.

22. Sharma C, Deutsch I, Horowitz DP, Hershman DL, Lewin SN, Lu YS et al. Patterns of care and treatment outcomes for elderly women diagnosed with cervical cancer. Cancer. 2012;118:3618-26.

23. Nogneira-Rodrigues A, de Melo AC, Graces AH, Paulino E, Alves FV, Vilaca Mdo N et al. Patterns of care and outcome of elderly women diagnosed with cervical cancer in the developing world. Int J Gynecol Cancer. 2016;26:1246-51.

24. Wright JD, Gibb RK, Geevarghese S, Powell MA, Herzog TJ, Mutch DG, et al.Cervical carcinoma in the elderly: an analysis of patterns of care andoutcome. Cancer. 2005;103:85-91.

25. Pinto A, De Filippi R, Frigeri F, et al. Aging and the hemopoietic system. Crit Rev Oncol Hematol. 2003;48(Suppl):S3-S12.

26. Hakim FT, Flomerfelt FA, Boyiadzis M, et al. Aging, immunity and cancer. Curr Opin Immunol. 2004;16:151-6.

27. Castle SC. Clinical relevance of age-related immune dysfunction. Clin Infect Dis. 2000;31:578-85.

28. Ellis RE. The distribution of active bone marrow in the adult. Phys Med Biol 1961;5:255–258.

29. Blomlie V, Rofstad EK, Skjonsberg A, et al. Female pelvic bone marrow: Serial MR imaging before, during, and after radiation therapy. Radiology 1995;194:537–543.

30. Sacks EL, Goris ML, Glatstein E, et al. Bone marrow regeneration following large field radiation: Influence of volume, age, dose, and time. Cancer 1978;42:1057–1065.

31. Rubin P, Landman S, Mayer E, et al. Bone marrow regeneration and extension after extended field irradiation in Hodgkin's disease. Cancer 1973;32: 699–711.

32. Sykes MP, Chu FC, Savel H, et al. The effects of varying dosages of irradiation upon sternal-marrow regeneration. Radiology 1964;83:1084–1088.

33. Mauch P, Constine L, Greenberger J, et al. Hematopoietic stem cell compartment: Acute and late effects of radiation therapy and chemotherapy. Int J Radiat Oncol Biol Phys 1995;31:1319–1339.

34. Ratanatharathorn V, Powers WE, Temple HT. Palliation of bone metastasis. In: Halperin EC, Perez CA, Brady LW, editors. Perez ans Brady's Principles and practice of radiation oncology. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.p.2387-9.

35. Varlotto J, Stevenson MA. Anemia, tumor hypoxemia, and the cancer patient. Int J Radiat Oncol Biol Phys. 2005;63:25-36.

36. Weiping Wang, Xiaorong Hou, Junfang Yan, Jie Shen, Xin Lian, Shuai Sun et al. Outcome and toxicity of radical radiotherapy or concurrent chemoradiotherapy for elderly cervical cancer women. BMC Cancer. 2017;17:510. 2017 Aug 1 [cited 2017 Oct 25]; . doi: 10.1186/s12885-017-3503-2 PMCID: PMC5540340.