Original Research: Retrospective analysis of patients with cancer of the cervix attending a radiotherapy outpatient department

Retrospective analysis of patients with cancer of the cervix attending a radiotherapy outpatient department: experience from a university-based hospital in eastern Uttar Pradesh, India

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Keywords: cancer of the cervix, retrospective analysis, epidemiology, radiotherapy, chemotherapy, toxicity, response rates

Abstract

Objective: A retrospective analysis of all patients with cancer of the cervix attending a radiotherapy outpatients department in a single unit from January 2005 to December 2006 was carried out to study their epidemiology, stage and status of presentation, compliance with treatment and follow-up, as well as response and complication rates.

Design: This was a retrospective study.

Setting and subjects: Four hundred and ninety-five consecutively registered patients with cancer of the cervix were included in the study, which was carried out between January 2007 and December 2008.

Outcome measures: The epidemiology, stage and status of presentation, compliance with treatment and follow-up, as well as the response and complication rates of the treated patients were the outcome measures.

Results: Most of the patients hailed from the various districts of Uttar Pradesh (58%) and Bihar (32%), India. The majority (> 50%) were aged 40-59 years. Stage information was available for 70% of the patients, of which stage 1 comprised 5%, stage 2, 36%; stage 3, 56%; and stage 4, 3%. Squamous cell carcinoma was the most common reported histopathology (~90%). A significant proportion of the women defaulted after registration, or after undergoing investigations (34%). Of the 65% cases planned for treatment, 50% initiated it, but only 35% completed it, according to protocol. Radical radiotherapy was planned for the majority of women (>90%) with or without chemotherapy. Compliance with follow-up was poor (26%). At the time of the analysis, 63% patients had a complete response, 12% residual disease, 16% progressive disease and 7% locoregional recurrence. Recorded late complications were mostly grade I and II bladder and rectal toxicity.

Conclusion: The outcome of this study will significantly help us to define region-specific strategies needed for the management of cervical cancer in eastern Uttar Pradesh, India.

Introduction

Cervical cancer is the fourth most common cancer that affects women worldwide, and the seventh overall. Of an estimated 528 000 new cases in 2012, approximately 85% occurred in less developed countries, of which one fifth was diagnosed in India. There were 266 000 deaths from cervical cancer in 2012, accounting for 7.5% of all female cancer deaths. Approximately 87% of the worldwide mortality for cervical cancer occurs in less developed countries.

The figures of cases of cervical cancer in India are mainly derived from the population-based cancer registries (PBCRs) and hospital-based cancer registries (HBCRs). PBCR demographics reveal that the incidence of cervical cancer is 30%, i.e. the proportion that is relative to all sites of cancer in females, in the Barshi (rural and expanded) registry, where it is the leading cancer, whereas in others, i.e. most other urban registries of Delhi, Bhopal and Chennai, it is 14-15%, where breast cancer is at the top of the list. Data from the HBCRs are...
a little different. Cervical cancer remains the leading cause in Bangalore (27.5%), Chennai (28.0%) and Dibrugarh (14.4%), while it is the second most common in Mumbai (15.5%) and Thiruvananthapuram (11.0%).

As of 2013, 70% of the Indian population lived in the rural belt of the country. The north-eastern districts of Tamil Nadu and Pondicherry, which have a high proportion of the rural population, have reported a very high incidence of cervical cancer. Ambillikai Cancer Registry has reported the second highest incidence of cervical cancer in the world.

Radiotherapy remains an effective treatment modality for all stages of cervical cancer, but radiotherapy treatment facilities in India remain woefully inadequate in handling the ever-increasing burden of cases diagnosed each year. Most cases present in the advanced stages of the disease. Treatment compliance and follow-up remain dismal in this part of the world.

The pre-invasive stage of cervical cancer lasts for a long period, and only a small proportion of cervical intraepithelial neoplasia (CIN) progresses to an invasive lesion. The appropriate management of CIN can prevent invasive cervical cancer. Thus, the detection of in situ cases or early stages of cancer remains key to decreasing cervical cancer mortality. Population-based screening with a 5-10 year interval, directed at high-risk groups, is the most realistic preventive method. In a recent reported trial by the Tata Memorial Hospital, Mumbai, performed on the rural population close to Mumbai, visual inspection, with 5% acetic acid, helped with a 31% reduction in cervical cancer mortality. The incidence of invasive cervical cancer after 12 years reduced in the screened arm and compliance with treatment improved in the screened group.

**Method**

The present study was carried out in the Department of Radiotherapy, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India, with effect from January 2007 to December 2008. The study comprised a retrospective analysis of patients with cervical cancer attending the radiotherapy outpatient department of a single unit from January 2005 to December 2006.

Patients were assessed as per the available records on their detailed clinical history, a complete clinical examination and investigations (haematological, biochemical and radiological), performed before the actual treatment plan, during treatment and at the time of follow-up. The majority of the patient population attending the institution had a histopathology report. Others were either referred to the Department of Gynaecology and Obstetrics for a cervical biopsy, or the biopsy was performed in the department itself. A review of the histopathological diagnosis was obtained from the Department of Pathology in some cases. All of the cases had been examined and staged by a radiation oncologist, according to International Federation of Gynecologists and Oncologists (FIGO) staging system.

The treatment policy depended on the FIGO stage and status of the first presentation of the patients. The usual policy was radical radiotherapy or adjuvant radiotherapy, with or without chemotherapy, followed by intracavitary radiotherapy (ICRT). External beam radiotherapy (EBRT) was delivered using appropriate portals. Parallel opposed anteroposterior-posteranterior (AP/PA) portals were used for patients with an inter portal distance (IPD) of < 20 cm or a four-field box technique for patients with an IPD > 20 cm. Radiotherapy planning was either carried out manually or on a simulator (Shimadzu), or on the treatment planning system (Rad Plan 2D). The standard field borders were the L4-L5 junction as the superior border, the lower most extent of the obturator foramen as the inferior border, modified according to the extent of vaginal involvement, and 1.5-2 cm lateral to the widest part of the pelvic brim as the lateral borders. The anterior and posterior borders were placed at the anterior part of the symphysis pubis and the S2-S3 junction, respectively. 15 x 15 cm² or 18 x 15 cm² AP/PA portals were used for manual planning. Treatment was delivered by the Co-60 Teletherapy® unit (Phoenix or Theratron 780E®). This was followed by the ICRT procedure, performed 7-10 days after completion of the EBRT.

Following completion of the EBRT, patients underwent evaluation for suitability for ICRT. The anatomical and geometrical conditions were noted, and the response to EBRT assessed. The dose for brachytherapy was prescribed at point A, defined by the Manchester system as 2 cm above the vaginal fornix and 2 cm lateral to the midline for patients with an intact cervix. The type of applicator used was Fletcher-Suit®, which includes small, medium, and large colpostats, depending on the clinical assessment of the vagina at the time of insertion. Orthogonal films were taken to verify the placement of the applicators and to perform the dosimetric plan. Insertion of the applicators was performed in the operating room. Packing is always performed to fix the applicators and to increase the distance between the sources and the posterior rectal wall and anterior bladder. The radioisotope source used was Cesium-137, with a low-dose-rate regimen and a manual or remote afterloading procedure. The dose rate at point A ranged from 0.44-0.99 Gy/hour, with a median of 0.68 Gy/hour. In post operative cases, segmented cylinder of appropriate diameter was used as per clinical assessment of the vaginal vault. Dose was prescribed at 0.5cm from the surface of the applicator.

Response was assessed by subjective and objective response at four weeks after treatment completion. Objective response was graded as complete response, residual disease, locoregional recurrence and progressive disease.
Patients were followed-up on a monthly basis for the first three months, three monthly for the next 1-2 years, and then at six monthly visits thereafter, until five years. During follow-up, response and toxicities were assessed clinically and managed appropriately.

Four hundred and ninety-five patients attending the radiotherapy outpatient department of a single unit were subjected to retrospective analysis of their demographics, stage and status of first presentation at the reporting institution, treatment compliance and follow-up, as well as their response and complication rates. The data were recorded on pre-designed proforma, managed on Excel® spreadsheets and the entries checked for errors. Thus, the obtained data was subjected to analysis.

Results

A total of 1 975 new cases at all of the cancer sites was registered under a single unit in our department from January 2005 to December 2006, of which 495 new cases of carcinoma of the cervix were included in the present study for retrospective analysis.

Table I: The patient demographics

| Demographics                  | n (%) |
|-------------------------------|-------|
| State                         |       |
| Uttar Pradesh                 | 292 (58.99) |
| Bihar                         | 161 (32.52) |
| Jharkhand                     | 20 (4.04) |
| Madhya Pradesh                | 17 (3.43) |
| Chhattisgarh                  | 4 (0.80) |
| Nepal                         | 1 (0.20) |
| Age group (years)             |       |
| 10-19                         | 1 (0.20) |
| 20-29                         | 7 (1.41) |
| 30-39                         | 74 (14.94) |
| 40-49                         | 159 (32.12) |
| 50-59                         | 138 (27.88) |
| 60-69                         | 93 (18.78) |
| 70+                           | 23 (4.65) |
| Stage                         |       |
| CIN                           | 3 (0.60) |
| IA                            | 15 (3.03) |
| IIA                           | 17 (3.43) |
| IIB                           | 105 (21.21) |
| IIIA                          | 6 (1.21) |
| IIIB                          | 186 (37.57) |
| IVA                           | 11 (2.22) |
| Unknown                       | 152 (30.70) |

CIN: cervical intraepithelial neoplasia

Table II: The plan details of the patients according to their stage and status of presentation

| Stage | n (%) |
|-------|-------|
| CIN   | 3 (0.87) |
| I     | 15 (4.37) |
| II    | 122 (35.56) |
| III   | 192 (55.97) |
| IV    | 11 (3.20) |

Most of the women hailed from various districts of the home and neighbouring states. Table I enumerates the patient demographics.

The median age of the women was 50 years. The majority were middle-aged, i.e. in the 4th and 5th decade of their lives), although a sizeable population was young (< 40 years).

Stage information was not available for 30% (n = 152) of the patients. These cases had received treatment at other centres, and the treatment record details were either unavailable or the patient had not been staged before therapeutic intervention. The majority of the remaining 70% presented with advanced-stage disease.

Sixty-six per cent of the women reporting at the hospital were new cases, having received no prior treatment, and 27% were postoperative, having undergone either a simple or Wertheim hysterectomy. Of the operated cases, 14% had residual disease, having undergone suboptimal surgery at other centres, and 15% women had recurrent disease as they had either not been advised to take, or had not undergone, adjuvant treatment post surgery. Six per cent of the patients had been referred for an ICRT application at our centre, after having receiving EBRT at another centre, for a segmented cylinder application (the postoperative cases,) or a Fletcher suit/Board of Radiation and Isotope Technology application for women with an intact cervix. Four cases of metastatic disease reported to the department, after having completed chemoradiotherapy at an outside centre (Table III).

Table III: The status of the patients on initial presentation (n = 945)

| Status | n (%) |
|--------|-------|
| New cases | 330 (66.67) |
| Prior treatment | 165 (33.33) |

Types of prior treatment received(n=165)

| Surgery | 135 (81.81) |
|---------|-------------|
| Post-surgery recurrence | 20 (12.41) |
| Post-surgery residual | 21 (13.21) |
| Chemotherapy | 9 (5.45) |
| Surgery plus EBRT | 7 (4.24) |
| EBRT | 4 (2.42) |
| Post-radiotherapy recurrence | 6 (3.63) |
| Post- (concurrent chemotherapy-radiotherapy) metastatic disease | 4 (2.42) |
Histopathological diagnosis was available for 84% of the cases (Table IV) amongst which most squamous cell carcinoma (SCC) (89%), followed by adenocarcinoma (4%), small cell (2%) and others (Table IV).

A treatment plan could not be generated for 34% of the women as they had defaulted after registration or after undergoing investigations. Of those for whom treatment was planned, 92% were to undergo radical radiotherapy, followed by brachytherapy. Fifty-four per cent received two cycles of neoadjuvant chemotherapy (NACT). Six patients were to undergo ICRT as they had been referred to our centre for this purpose. Nine patients were to undergo two applications of ICRT, followed by EBRT as they had early-stage disease (IB1, IIA) (Table V).

The dose of EBRT was 46 Gy in 23 fractions at 2 Gy per fraction, completed over four-and-a-half weeks, followed by an ICRT dosage of 2 900 cGy (low-dose rate) one week later. Postoperative patients received the same EBRT dose followed by a ICRT dosage of 1 500 cGy after a gap of 7-10 days. Six patients who had been treated at outside centres and referred to us for brachytherapy were prescribed 2 500 cGy as the low-dose rate. They had received 50 Gy in 25 fractions over five-and-a-half weeks as EBRT. The protocol in our centre for early-stage disease (FIGO stage IA, IB1 and IIA) is to treat with ICRT first, followed by EBRT. Nine cases received two intracavitary applications of 35 Gy each, at an interval of 7-10 days, followed by an EBRT dose of 30 Gy in 15 fractions over three weeks, with midline shielding after three fractions. The chemotherapy schedule used was a three-drug regimen of paclitaxel, carboplatin and 5-FU. Carboplatin and 5-FU were given at a dose of area under curve 1.5 and 500 mg/m² on day 1, and paclitaxel 80 mg/m² on day 2.

Of the 495 patients, 250 of the women started the prescribed treatment plan and 175 completed it (Table VI).

One hundred and fifty-five patients out of 495 (31%) had attended at least one follow-up at the time of the analysis. A total of 129 out of 495 (26%) patients had attended the radiotherapy outpatient department for follow-up, either at regular (as per protocol) or irregular intervals. The last follow-up of the patients ranged from 3-40 months, following treatment completion. At the time of analysis, 99 (63.87%) patients had no evidence of disease; 19 (12.25%) patients residual disease, 26 (16.77%) progressive disease (the majority with liver and bone metastasis), and 11 (7.09%) locoregional recurrence (Table VII a and b).
Early and late toxicities were documented according to the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer toxicity grading criteria. Early toxicities encountered during radiotherapy were grade 1 and 2 proctitis and cystitis, treated with parasympatholytic agents and alkaline syrup, or urinary anaesthetic agents, respectively.

Late toxicities of varying grades were recorded in approximately 60% of the patients. The majority had grade I proctitis, treated effectively with stool softeners and/or steroid enemas. The median time to proctitis was 10 months following the completion of radiotherapy, and most of the toxicities appeared within 8-16 months. Seventeen per cent of the patients developed grade 2 rectal toxicity. They were referred to the gastroenterology department for formaldehyde instillation. Intestinal obstruction (grade III toxicity) that required laparotomy was documented in one patient. Three women developed a perforation or fistula (grade IV), attributed to radiation as there was no evidence of local disease. The bladder toxicity incidence rates were comparatively lower than those of rectal toxicity. Most patients presented with grade 1 and 2 toxicities at the routine follow-up. They were managed with antifibrinolytics, i.e. tranexamic acid, or urinary anaesthetic agents. Typically, they appeared from 18-40 months, with a median duration of 26 months. Grade III bladder toxicity was seen in 5% of the patients, who were referred to the urology department for bladder irrigation or urethral dilatation. Cystoscopy was performed when required. Grade IV bladder toxicity was not noted in any of the patients (Table VIII).

Discussion

Cervical cancer accounted for 44% (n = 495) of all the cancer cases (n = 1 128, total registration = 1 975) registered during this period. The global trends reveal that African countries like Malawi (75.9), Mozambique (65.0) and other southern [Zambia (58) and Zimbabwe (56)], and central African countries are high-risk regions (with the age-standardised rates of over 30 per 100,000 across 10 age groups). Countries with low rates include Australia and New-Zealand (5.5) and West Asia (4.4).

The median age of the population was 50 years (range 18-80 years). The majority (> 50%) were in the fourth and fifth decade of life. Approximately 20% were young (< 40 years). Demographics from HBCRs show that 30-40% of cases lie in the range of 40-60 years across all registries. It was revealed in a study from rural India by Thulaseedharan et al that the maximum number of cervical cancers are diagnosed in the fourth and fifth decade of life. According to the Surveillance, Epidemiology, and End Results Program (SEER) statistics, most women with cervical cancer are identified before the age of 50. The median age was 49 from 2006-2010. Older women remain at risk, and more than 20% of new cases are diagnosed in women aged 65 years and older. By contrast, cervical cancer in the UK is common in women aged 15-34 years, and is accountable for 16% of all cancer that is diagnosed in this age group. It is primarily a disease of the young. Sixty-two per cent of registrations are by those aged ≤ 50 years. The peak age of diagnosis is 25-29 years.

SCC was the most frequent histopathology reported (89%), of which grade I comprised 32% of all cases. Adenocarcinoma was reported in 4.5% of cases. According to the SEER statistics,
SCCs account for 66% of cases, adenocarcinomas 28% and 6% are other subtypes. Approximately two thirds of the cancers are SCCs in the UK, 15% are adenocarcinomas, and others are poorly differentiated. A retrospective analysis of cervical cancer cases performed in the Post Graduate Institute of Medical Education and Research, Chandigarh, India, between 1996 and 2001 revealed SCCs to be the most common, accounting for 96%, followed by adenocarcinoma (2.6%) and others (1.3%).

In India, 85-90% of cervical cancer cases are SCC, and human papillomavirus (HPV) 16 is the most prevalent type among them, compared to other parts of the world where the proportion of HPV16 is much lower, and is up to 70% when both HPV16 and 18 are considered. In India, the prevalence of HPV16 alone in cervical cancer is 70-90%, while the occurrence of HPV18 varies from 3-20%. The higher proportion of adenocarcinoma cases has been observed in those areas where the incidence of cervical cancer is low. It accounts for more than 25% of all cervical cancer cases in some Western countries. Unlike SCC, in which HPV16 contributes up to 70% of cases, in adenocarcinoma, infection with HPV18 is reported to be more prevalent worldwide, i.e. > 86%. In contrast, only 10-15% of cervical cancer cases in India are adenocarcinoma, and HPV16 is the most prevalent type, although it is less frequent than that found in SCC, i.e. 42% vs. 70-90%.

A majority (95%) presented with advanced stage disease with stage IIB and IIIB, accounting for 36% and 56% of all cases, respectively. HBCRs reveal a similar picture, of roughly 75% of patients presenting with regional disease on first presentation. In their analysis, Saibishkumar et al. reported high percentages of patients with stage IIB disease (67%). A study on factors associated with the late diagnosis of cervical cancer in Nepal; revealed illiteracy, older age and residence in remote areas to be some of the factors. The impact of socio-economic factors pertaining to the stage of cervical cancer patients at diagnosis and the time to report to a major cancer hospital was also analysed in a similar study from South India. Those widowed or divorced, or having a lower level of education, reported to the hospital late. They enumerated that such a trend exists because there is no support from families. Those with little to no education do not understand the implications of the disease process.

Most of the cases presented as new cases, i.e. they had not received any prior treatment. Approximately 27% of the patients were registered after having undergone surgery outside. Of these, a significant proportion had residual or recurrent disease. This is because most of these patients had received treatment at the hands of surgeons with inadequate skills or knowledge of oncology.

> 90% of the women were treated with adjuvant radiotherapy (EBRT plus ICRT), of whom 54% received NACT. So radiotherapy as a single modality, or in combination, was the most common mode of treatment used with curative intent. The data across the HBCRs give a similar picture, as radiotherapy is reported as the most common modality of treatment rendered to the patients (75-90%). Most of the cases presented with advanced-stage bulky tumours and long waits for radiotherapy start dates, the poor performance status of the patients made them ineligible for concurrent chemoradiotherapy, so patients were treated with a neoadjuvant regimen of two cycles of paclitaxel, carboplatin and 5FU, given at an interval of 21 days, followed by radical radiotherapy 2-3 weeks later. Several trials have examined the role of NACT in cervical cancer. Although a meta-analysis of 21 randomised trials showed no improvement in overall survival with NACT, an association between outcome and short cycle length, or platinum with dose intensity of more than 25 mg/m2/week was established. The combination of taxane and platinum has long been established as being effective in advanced or recurrent cervical cancer, with response rates of roughly 50%. This combination has also been reported to be effective in the neoadjuvant setting, with response rates of approximately 90-95%. Cisplatin and paclitaxel require a longer infusion time than a carboplatin or paclitaxel combination, which has been demonstrated to have acceptable toxicity and promising activity. Single-agent 5FU has modest activity (about 10%) in carcinoma of the cervix. Cisplatin and 5FU are known to act synergistically, and have been reported to be effective in metastatic and recurrent cervical cancer. Thus, our patients were treated with combination chemotherapy of carboplatin, paclitaxel and 5FU, using the previously described protocol.

A treatment plan was generated for 65% of the total registered patients, but only 35% completed it. These figures reveal the lack of awareness and compliance with treatment in the rural population of our country. HBCRs also reveal a similar picture. Fifty per cent of patients did not receive any treatment according to the Chennai registry. 47% according to the Mumbai registry and 37% according to the Bangalore registry, which is interesting to note since all of these registries have a more urban population registration than other parts of the country. A retrospective analysis of cancer cervix patients carried out in Kolkata by Mandal and Roy showed a similar picture of almost 40% of patients not undergoing any treatment at all.

Possible reasons for a high default rate could be clinical, including death or relief from the symptoms; social and structural, including lack of transportation, distance to the clinic and child care responsibilities; as well as financial.

Twenty-six per cent of the patients (of the total registration) had attended the radiotherapy outpatient department for follow-up either at regular (as per the protocol) or irregular intervals at the time of analysis. At the time of the analysis,
63% of the patients had a complete response with no evidence of disease, 12% residual disease, 16% metastatic disease (the majority having liver and bone metastasis), and 7% locoregional recurrence.

A look into the patterns of compliance with treatment and follow-up of the 1,003 patients with cervical cancer, performed in Kolkata, by Mandal and Roy, revealed that only 5% patients were on follow-up at six years post completion of treatment, and that 84% had been lost to follow-up. They also looked into possible reasons for noncompliance with follow-up. Financial constraints and health issues were reported to be the primary causes in their group of patients. Uma Devi, in her study carried out on the current status of gynaecological cancer care in India, stated that in the Kidwai Memorial Institute of Oncology, approximately 50% of the patients were compliant with treatment, less than 30% had defaulted during adjuvant therapy, and 20% had defaulted after undergoing preliminary investigations. She also stated that overall, 30% of the patients completed follow-up for three years in the regional cancer centres, and 70-80% in comprehensive cancer centres.

Most patients encountered grade 1 and 2 bladder and rectal toxicities, which were treated effectively. Grade 3 and 4 bladder and rectal toxicities were 5% and 0%, and 0.6% and 2%, respectively. Perez et al retrospectively evaluated 1,456 patients with stages IB-IVA, treated with EBRT plus two low-dose rate ICRT insertions, to deliver 70-90 Gy to point A and correlated doses with sequelae. Median follow-up was 11 years. Cystitis and proctitis (0.7-3.0%) were the most frequent grade 2 sequelae. Vesicovaginal fistula (0.6-2.0%) in patients with stage I-III tumours, rectovaginal fistula (0.8-3.0%) and intestinal obstruction (0.8-4.0%) were the most common grade 3 sequelae. Lanciano et al reported on a 10% and 14% actuarial incidence of major complications at three and five years, respectively, in 1,558 patients with stage IB cervical carcinoma, treated with radiotherapy in the Patterns of Care Study. Most complications occurred in the large and small bowels (61%). Only 0.8% of the patients treated with radiotherapy died as a result of treatment-related complications.

Our study revealed a higher incidence of late complications, mainly rectal complications. The probable reason might be that all of the these patients were treated on Cobalt-60, mostly with parallel opposed AP/PA fields, and subsequently by low-dose rate brachytherapy, which involves the risk of underpacking (mainly posterior vaginal packing) and the displacement of applicators owing to the long treatment times.

In conclusion, this study was undertaken to provide insight into the cervical cancer burden in the eastern part of the country. The majority of the patients hailed from remote villages. A large proportion of the patients presented in advanced stages of the disease, and were treated with radical radiotherapy, with or without chemotherapy.

Compliance was poor. The response and complication rates were comparable with other datasets, although there were more rectal complications. In the absence of a cancer registry in Uttar Pradesh, such studies will help us to formulate region-specific cancer control policies in this part of the country.

Declarations

The work is attributed to Department of Radiotherapy and Radiation Medicine, Institute of Medical Sciences, Banaras Hindu University, Uttar Pradesh, India.

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