RESEARCH COMMUNICATION

Postoperative Radiotherapy Following Inadvertent Simple Hysterectomy versus Radical Hysterectomy for Cervical Carcinoma

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Abstract

Purpose: For cervical carcinoma, postoperative radiation therapy (PORT) following radical hysterectomy (RH) is indicated for certain adverse pathological factors. Simple hysterectomy (SH) is considered inadequate treatment for invasive cervical carcinoma and PORT is required for all such cases. Clinical outcome of patients receiving PORT following SH and RH may be different. The aim of our retrospective study is to compare the results of PORT following inadvertent SH or RH in cervical carcinoma. **Materials and Methods**: During year s2003-2005, we treated 83 patients with cervical carcinoma with PORT following either SH (Group SH, 33 patients) or RH (Group RH, 50 patients). All patients were treated with pelvic external beam radiation therapy (EBRT) followed by intravaginal brachytherapy (IVBT). The endpoints of the study were local control, recurrence free survival (RFS) and delayed complications. **Results**: Median follow period up was 34 months (range 2-75 months). Local control rate observed in Gp SH and RH was 70% and 88% respectively with a p value of <0.05. Cumulative 5-year overall survival (OS) for combined group was 62%. Group RH patients had significantly better 5-year RFS than Group SH patients (72% and 49% respectively; p value 0.04). The frequency of Grade III-IV toxicity (bladder, rectum, and bowel) in Group SH versus Group RH was 6% vs 8% respectively (p value 0.1). The pedal lymph edema was higher in Group RH patients (10% vs 3%, p value <0.05). **Conclusion**: PORT provides greater clinical benefit in patients who had undergone RH than SH for early stage invasive cervical carcinoma.

Keywords: Cervical carcinoma; inadvertent hysterectomy; radical hysterectomy; postoperative radiotherapy

Introduction

Cervical carcinoma is the commonest cancer in females in developing countries, including parts of India (Population based cancer registry, Delhi, 2007). Though majority of patients present in advanced inoperable stages of the disease, patients with early stages still constitute a sizable population (Rath and Mohanti, 2000). Both RH and definitive radiation therapy (RT) are standard treatment options with equal results for early stage disease (Kavanagh and Perez, 2008). Following RH, PORT is indicated for patients having adverse pathological factors like positive pelvic nodes, parametrial infiltration, positive margins, deep stromal invasion etc. (Sedlis et al., 1999; Atkovar et al., 1995; Hart et al., 1997; Ghia et al., 2010). SH is considered inadequate surgery for invasive cervical carcinoma (Davy et al., 1977; Hopkins et al., 1990) and subsequent therapy is required for all such cases (Durrance et al., 1968; Andras et al., 1973; Perkins et al., 1984; Kinney et al., 1992; Orr et al., 1986). Inadvertent SH, performed due to improper preoperative workup and

various other factors, still remains a problem. Magnitude of this problem may be larger in developing countries like India because of several factors like 1) lack of Pap's smear screening 2) improper diagnostic work up before surgery 3) limited availability of dedicated cancer centers equipped with surgical and radiation oncology facilities. PORT for patients undergoing inadvertent SH has been shown to be beneficial (Durrance et al., 1968; Andras et al., 1973; Perkins et al., 1984; Chen et al., 2003; Saibishkumar et al., 2005). Therefore, PORT following inadvertent SH as well as RH remains an important adjuvant treatment modality. Though the results of PORT have been studied separately for the patients undergoing inadvertent SH (Durrance et al., 1968; Andras et al., 1973; Perkins et al., 1984; Chen et al., 2003; Saibishkumar et al., 2005) and RH (Sedlis et al., 1999; Atkovar et al., 1995; Hart et al., 1997; Ghia et al., 2010), there is limited literature comparing the prognosis and outcome of these two groups of patients. Indeed the usual perception is that SH is an inadequate treatment for early cervical carcinoma patients and PORT may not compensate for it; but on the other hand, RH

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patients receiving PORT have obvious adverse features (positive nodes, parametrial infiltration, positive surgical margins etc.) which relates to poor outcome of these patients. It is commonly believed by both gynecological oncologists and cervical cancer patients that PORT in all cases following SH will result in poorer outcome as compared to selective cases with adverse factors requiring PORT following RH. Contrary to this common belief, a study by Munstedt et al (Munstedt et al., 2004) has shown inferior survival with PORT in patients who had undergone RH. The study by Munstedt et al (Munstedt et al., 2004) stimulated us to analyze and compare the clinical outcome of these two groups of patients treated by PORT at our institution. The endpoints of the study were local control, recurrence free survival and delayed complications.

Materials and Methods

For this retrospective analysis, we retrieved the case records of all the cervical carcinoma patients who received PORT at our center between the years 2003-2005. From each case record, we extracted the information regarding the patient's demography, clinical details, diagnosis, treatment given, survival and complications. The patients were divided into two groups: Group SH comprising of patients receiving PORT after SH; and Group RH comprising of patients receiving PORT after RH. RH was defined as removal of uterus along with ovaries, cervix, and upper part of vagina, bilateral parametria and pelvic nodes. SH was defined as removal of uterus (with or without ovaries) and cervix without removal of parametrium, pelvic nodes and part of vagina; or any other form of suboptimal surgery. Since all the patients in Group SH were operated outside and referred to us for PORT, there was limited information regarding preoperative clinical, radiological and pathological details. Therefore, the stage of the disease could not be ascertained and we have not analyzed the data with respect to the stage of the disease. Patients who had non-carcinoma histology and those who underwent part of PORT course outside our hospital were excluded from present analysis.

The initial post surgery workup of the patients consisted of detailed clinical examination in the gynecologic oncology clinic by a team co mprising of gynecologist and radiation oncologist. Each patient was subjected to various routine hematological and radiological investigations. CT/MRI scan of the abdomino-pelvic region and cysto-sigmoidoscopy, if necessary, were done for all the patients who were operated outside.

The various indications of PORT at our center were: 1) Inadvertent surgery, 2) pathologically positive node, 3) positive surgical margins, 4) parametrial infiltration, 5) deep stromal invasion and 6) bulky disease (>4.0 cm). The PORT consisted of a combination of EBRT and IVBT. Weekly chemotherapy (Cisplatin dose 40 mg/m2) was administered during the course of EBRT to patients who had gross residual disease after surgery.

EBRT

Pelvic EBRT was carried out on Cobalt-60 or Linear Accelerator (15-18 MV Photons). The dose schedule consisted of 40 Gy in 22 fractions over 5.5 weeks to whole pelvis with four field box technique followed by 10 Gy in 5 fractions over 5 days with midline shield (split field). X-ray simulation was done for each patient on Oldelft Simulator (Nucletron). For AP-PA portals, superior border was kept at L4-L5 junction, inferior border at 3 cm below the vaginal cuff or at the bottom of obturator foramina and the lateral border at 2 cm lateral to bony pelvic brim. For lateral portals, superior and inferior borders were kept same as in AP-PA portals; anterior border was placed anterior to pubic symphysis; and posterior border at S2-S3 level.

IVBT

After the completion of EBRT, IVBT was performed to treat vaginal cuff using ovoids. The dose of IVBT was prescribed at a depth of 0.5 cm from the surface of the ovoids. A dose of 30 Gy by low dose rate (LDR) or 8 Gy X 2 (weekly) by high dose rate (HDR) was delivered using remote after loading unit. Any patient having gross disease at the time of IVBT was taken up for perineal interstitial brachytherapy implant. Two such implants were performed one week apart to deliver a total dose of 16 Gy by HDR (8 Gy X 2).

Follow up and Clinical Assessment

Patients were followed every month till 6 months, then every 2 months till one year and then subsequently every 3 months till 2 years. Thereafter follow up was done every 6 months. At every visit, clinical examination was performed and, if necessary, CT/MRI scans, to assess the disease status and toxicity. PET scan was also done if there was a suspicion of disease on clinical/radiological examination. The late toxicity was assessed according to Radiation Therapy Oncology Group (RTOG) criteria (Cox et al., 1995).

Statistical Analysis

Using the statistical software SPSS, version 11.5, the OS and RFS was calculated by Kaplan Meier (Kaplan and Meier, 1958) survival method. The RFS was defined as period from the date of completion of treatment to the date of recurrence. Each patient, who lost follow up after a certain period was censored at that point of time for survival analysis. The survival and late toxicity rates of the two groups were compared. Log rank test was used to find out the p value and a value of <0.05 was considered significant.

Results

A total of 83 patients records were retrieved for this analysis. Of them, 33 patients belonged to Group SH and 50 patients belonged to Group RH. Median age and histological types were comparable in the two groups. A stage wise distribution of Group RH patients was: stage IB1, 20; stage IB2, 16 and stage IIA, 14 patients. Postoperative histopathological examination revealed parametrial infiltration in 4 patients, positive margin in 2 patients, lymph node metastases in 18 patients and deep stromal invasion in 26 patients. A total of 326 nodes

were removed in 50 patients of Group RH (6.7 nodes per patient) and 66 of them (20%) were pathologically positive in 18 patients (3.7 per patient). Seventeen patients had more than one adverse factor.

Regarding postoperative treatment (see Table 1), one patient in Group SH and two patients in Group RH could not complete the prescribed EBRT dose of 50 Gy. Four patients in Group SH had residual growth thicker than 5 mm after EBRT and therefore underwent interstitial brachytherapy instead of IVBT.

Disease Status and survival

Median follow up period for all patients, Gp SH patients and Gp RH patients was 34, 31 and 40 months respectively. Eleven patients in Group SH and 8 patients in Group RH had disease recurrence. Local control (pelvic control) rate observed in Group SH and RH was 70% and 88% respectively with a p value of <0.05. One patient in Group SH had metastases in lung as well as vertebral bones while 2 patients in Group RH had metastases in brain and liver (one each). The 5-year cumulative overall survival for all patients was 62% . As shown in Figure 1, the 5-year RFS was significantly better in Group RH than Group SH (72% vs 49%, p value 0.04).

Delayed Toxicity

Table 1 also shows the frequency and pattern of

Table 1. Details of Postoperative Treatment and Outcome

Characteristics	Group SH	Group RH
No. of patients	33	50
EBRT	33	50
Dose range (Gy)	48-50	46-50
Duration of RT (weeks)	5.5-7	5-7
Brachytherapy		
IVBT with ovoids	29	50
LDR	16	33
HDR	13	17
Interstitial BT	4	0
Concurrent chemotherapy	10	4
Median no. of cycles	5	5
Disease free	22 (67)	42 (84)
Recurrence	11 (33)	8 (16)
Time of recurrence (months)		
Median	10	14
Range	2-32	5-20
Site of recurrence		
Pelvis	10 (30)	6 (12)
Distant	1	2
lung	1	
brain	-	1
bone	1	
liver	-	1
Toxicity	6 (18)	15 (30)
Pedal lymphoedema	1 (3)	5 (10)
Vaginal stenosis	3 (9)	6 (12)
Cystitis (grade III-IV)	1 (3)	2 (4)
Proctitis (grade III-IV)	1 (3)	1 (2)
Intestinal Obstruction	0	1 (2)

SH, Simple hysterectomy; RH, Radical hysterectomy; EBRT, External beam radiation therapy; RT, Radiation therapy; IVBT, Intravaginal brachytherapy; BT, Brachytherapy
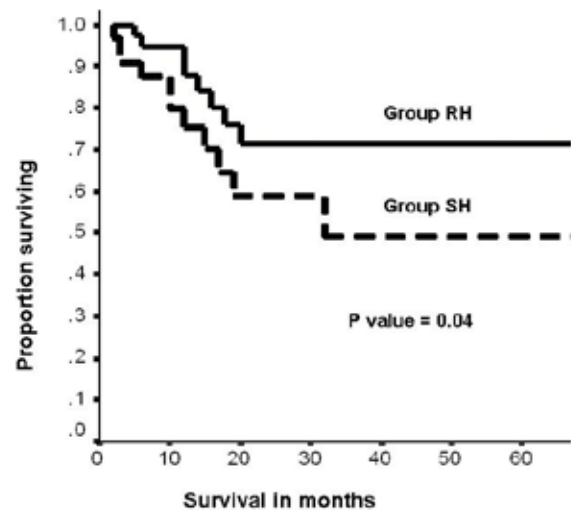

Figure 1. Kaplan Meier Curves Showing Recurrence-free Survival of Gp SH and Gp RH Patients

delayed toxicity. The frequency of Grade III-IV toxicity (bladder, rectum, and bowel) in Group SH versus Group RH was 6% vs 8% respectively (p value 0.1). The pedal lymph edema was significantly higher in Group RH patients (10% vs 3%, p value <0.05). Vaginal stenosis was almost similar in the two groups.

Discussion

RH alone can provide satisfactory results for most patients with early stage cervical cancer, but some patients are at high risk of recurrence due to adverse clinical and pathological factors. A Gynecologic Oncology Group (GOG) study of 575 women estimated that such risk factors existed in 25% of all Stage IB cancers and these factors increased the risk of recurrence from 2% to 31% at 3 years (Delgado et al., 1990). In the 1990s, the role of PORT for high risk cervical cancer was clarified by many trials (Sedlis et al., 1999; Atkovar et al., 1995; Hart et al., 1997). Even though RH is the recommended surgical procedure for early stage cervical carcinoma (except stage IA), still a considerable number of patients undergo inadvertent SH. According to a German study (Munstedt et al., 2002), this number is about 15%. Various studies from different countries have shown varying reasons for inadvertent SH (Munstedt et al., 2004). Main reasons noticed in these studies are: lack of preoperative PAP smear, deliberate hysterectomy for grossly invasive cancer, inadequate evaluation of an abnormal PAP smear or cervical biopsy, failure to perform a cone biopsy when indicated, and emergency operation because of bleeding (Munstedt et al., 2004). Irrespective of the reason, SH for invasive cervical carcinoma is considered a suboptimal treatment and in the absence of subsequent therapy with RT or parametriectomy, 5-year survival has been reported to be 42-60% (Jones and Jones, 1943).

Patients treated by inadvertent SH and those treated by RH having adverse factors carry poor prognosis. Both these groups of patients benefit from PORT as shown in several studies. (Durrance et al., 1968; Andras et al., 1973; Perkins et al., 1984; Atkovar et al., 1995; Hart et al., 1997;

Table 2. Comparison of Our with Munstedts' Study

Characteristics		Present study	Munstedts' study
No. of patients	Total	83	199
	Gp SH	33	80
	GP RH	50	119
Histology (SCC)	Gp SH	33 (91)	51 (69)
	Gp RH	45 (90)	91 (83)
Residual disease after surgery			
	Gp SH	10 (30)	0
	Gp RH	4 (8)	0
Dose of EBRT		46-50 Gy	46-60 Gy
Median follow up (months)			
	Gp SH	32	74
	Gp RH	40	98
Local recurrence rate			
	Gp SH	30%	15%
	Gp RH	12%	32%
5-year DFS	Gp SH	49%	Better survival (p <0.002)
	Gp RH	72%	
Delayed toxicity	Gp SH	18%	Not reported
	Gp RH	30%	

Numbers in parenthesis represent percentages

Sedlis et al., 1999; Chen et al., 2003; Saibishkumar et al., 2005; Ghia et al., 2010). But which group benefit more, in terms of survival and treatment related morbidity, is not yet clear since it has been rarely studied. Our results have shown that survival of cervical cancer patients treated by SH is poor even if they receive PORT. On the other hand, patients treated by RH benefit more with PORT even if they have adverse pathological features.

Though the results of PORT in these two groups have been studied separately but Munstedts' study (Munstedt et al., 2004) is the only study in the literature so far which has compared the outcome of these two groups. They had reported the series of 288 patients who received PORT following radical RH or SH. They divided these patients into three groups: RH alone (89 patients), RH plus PORT (119 patients), and SH plus PORT (80 patients). Disease free survival was significantly better in patients treated by RH alone, followed by SH plus PORT, and then RH plus PORT (P < 0.002). The local recurrence in patients treated by RH plus PORT was significantly higher than who received PORT following SH (p < 0.001).

Ours is the second such study, after the study by Munstedt et al (2004), till today. Though the number of patients in our study is smaller as compared to Munstedts' study, it is worth comparing the results of these two studies (Table 2). The results of Munstedts' study are in contrast to our results. They observed that PORT provided significantly better survival in Group SH than Group RH while we observed the reverse. The inferior results with PORT following SH in our study may be attributed to the fact 30% patients in Group SH had residual disease after SH as compared to 8% in Group RH. Additionally, all patients in Group SH had surgery outside and due to preoperative improper preoperative workup; some patients could have had advanced stage disease. Saibishkumar et al (Saibishkumar et al., 2005) too observed, in their series of 105 patients treated by salvage RT after inadequate surgery, that subset of patients having gross residual

disease had poor outcome (5-year disease free survival, 46.9%).

The doses and techniques of PORT have been more or less similar in the two groups of our study. Chemotherapy was added to the PORT in 30% and 8% of patients in Group SH and Group RH respectively, presenting with gross residual diseases. Yet the survival was inferior in the Group SH. Re-surgery in the form of parametriectomy plus lymphadenectomy is the other option suggested in the literature for patients who had inadvertent SH (Kinney et al., 1992; Orr et al., 1986). We would possibly explore that option in future in our setup to improve our results with PORT following SH. Simultaneously, we discourage the use of SH in invasive cervical cancer.

Although overall delayed morbidity in Group RH was higher as compared to Group SH (30% vs 18%) in our series, but grade III-IV bladder and rectal toxicity was same (6%). The incidence of vaginal stenosis and pedal lymph-edema was higher in Group RH mainly because of more extensive nature of surgery. Munstedt et al (Munstedt et al., 2004) have not mentioned the toxicity data in their report. However our delayed toxicity pattern and frequency has been comparable to other series (Andras et al., 1973; Perkins et al., 1984; Saibishkumar et al., 2005) in the literature. The toxicity rates may be further reduced by use of intensity modulated radiation therapy (IMRT), as has been shown in many studies (Portelance et al., 2001; D'Souza et al., 2005).

The addition of concurrent chemotherapy to PORT has been suggested in patients showing adverse features after RH patients (Peters et al., 2000). Due to our institutional policy, we did not follow the routine use chemo-radiotherapy in Group RH patients in our study. We use postoperative chemo-radiotherapy selectively for patients presenting with gross disease after surgery.

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