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Post operative Radiotherapy in Carcinoma Endometrium - KMIO Experience (A Retrospective Study)

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Purpose: *To compare the outcomes for postoperative endometrial cancer treated with adjuvant radiotherapy.* ***Methods:*** *68 patients with stage I to III endometrial cancer treated with Radical hysterectomy ± Pelvic lymph node dissection followed by brachytherapy or with a combination of external beam radiotherapy and brachytherapy were retrospectively analysed. Comprehensive surgical staging and pelvic lymph node dissection was done in 94% of patients .Teletherapy and Brachytherapy was used in 78% cases, while only brachytherapy was used in the adjuvant setting in 22%cases.HDR brachytherapy was used in 63% cases and LDR brachytherapy in 37% cases. Local control was evaluated in both the brachytherapy groups.* ***Results:*** *For all stages combined, the local control was achieved in 77% patients in the HDR brachytherapy group and in 88% of the LDR brachytherapy group.* ***Conclusion:*** *The local control was significantly better in the LDR group when compared to the HDR group. The mean survival and the median survival is better in the HDR group as compared to the LDR group. The subgroups with grade 3 tumors with deep myometrial invasion were benefitted by Teletherapy followed by Brachytherapy. Good local control was seen in patients who received HDR- 6Gy*3 or 7Gy*2 and LDR-30Gy to 0.5cm.*

Keywords: Endometrial carcinoma, High dose rate, Low dose rate, Brachytherapy, Radiotherapy.

1. Introduction

The estimated number of new cancers of the endometrium is around 49,560 cases a year and the deaths in the same group account to about 8,190 cases according to the American cancer society, Surveillance Research,2013. Endometrial carcinoma is the most common gynaecological cancer in developed countries and second most common in developing countries.(1)

The most significant prognostic factors which predicted overall survival with high concordance probability were age, grade, histologic type, number of lymph nodes removed and surgical staging.(2) More than 90% of cases occur in women older than 50 years of age, with a median age of 63 years. Endometrioid adenocarcinoma represent 80% of endometrial carcinomas.

Traditionally, the surgical approach consists of radical hysterectomy with bilateral salpingo-oophorectomy and with or without pelvic lymphadenectomy.(3)

External beam radiation therapy (EBRT) and/or brachytherapy play an important role in the postoperative adjuvant therapy of selected patients of carcinoma endometrium. Brachytherapy is increasingly being delivered by High dose rate (HDR) techniques worldwide as compared to the LDR technique which was predominant in the past. However there are no standard recommendations. Platinum based chemotherapy can be considered in stage I G3 with adverse risk factors (patient age, lympho vascular space invasion and high tumour volume) and in patients with stage II-III.

The present study has been done to retrospectively analyse the outcomes of radiotherapy in the adjuvant setting for the treatment of endometrial cancer.

2. Methods and Materials

A total of 68 patients with clinically and histologically proven carcinoma of the endometrium at KMIO(Kidwai Memorial Institute of Oncology), between 2007-2011 were analysed.Patients were treated by post hysterectomy ± pelvic lymphadenectomy and post op external beam radiotherapy ± brachytherapy.

All the patients were clinically examined and histological confirmation was obtained prior to initiation of treatment. They were all staged according to the International Federation of Gynaecology and Obstetrics(FIGO) classification.

The post hysterectomy specimens were histopathologically reviewed and were graded as well differentiated (Grade 1),moderately differentiated (Grade 2), poorly differentiated (Grade 3). Histologically they were categorised as adenocarcinoma, endometrioid adenocarcinoma, clear cell sarcoma , adeno squamous carcinoma and others.

The patients received a combination of external beam radiotherapy and brachytherapy or brachytherapy alone based on the stage and the grade of the tumour. The patients were divided into two groups, one receiving LDR brachytherapy and the other receiving HDR brachytherapy.

LDR brachytherapy was given to 25 patients(36.8%)while HDR brachytherapy was given to 43 patients(63.2%).The stage distribution according to FIGO criteria was as follows: Stage I(66.1%),Stage II(20.6%),Stage III(13.2%).With respect to the groups in the LDR group the distribution was as follows: Stage I(60%),Stage II(28%),Stage III(12%) and in the HDR group: Stage I(70%),Stage II(16%),Stage III(14%).The distribution of patients by tumour histology, tumour grade, the surgical stage are shown in the tables.

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3. Treatment Methodology

Surgery: An extra fascial Total Abdominal Hysterectomy and bilateral salpingo-oophorectomy along with a pelvic lymphadenectomy was done in majority of the patients.

External Beam Radiotherapy: All the patients were treated with Radiotherapy in the adjuvant setting. External pelvic irradiation was given in a cobalt machine or with a linear accelerator with parallel opposed anterior and posterior portals or a 4 field box technique. The dose per fraction was 1.8 to 2 Gy to a total dose of 45-50.4 Gy.

LDR brachytherapy or HDR brachytherapy was done following External Beam radiation or Brachytherapy alone was used in the adjuvant setting. LDR brachytherapy was done with Caesium-137 using a vaginal cylinder or Modified Fletcher Suit after loading colpostats (semi-small, small and medium ovoids) depending on the anatomy of the vagina at the time of application.
The dose prescription was usually 20-30 Gy to the surface of the vaginal mucosa and was given over a 15-36hrs.

HDR brachytherapy was delivered with HDR colopostats or vaginal cylinder and the prescription dose was 5.5-8Gy delivered in 2-3 fractions with a minimum inter fraction gap of 6 hours. HDR brachytherapy was delivered using a Gamma Med plus brachytherapy device using Iridium 192 source.

During brachytherapy adequate vaginal packing was done to reduce the bladder and the rectal doses when colpostats were used. No packing was done when vaginal cylinders were used. The intent of treatment was to treat the upper third of vagina.

4. Statistical Analysis

Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance.

Study design: A Comparative observational clinical study

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis) on metric parameters. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. Kaplan Meier Function analysis is performed to find the mean survival in days in two groups.

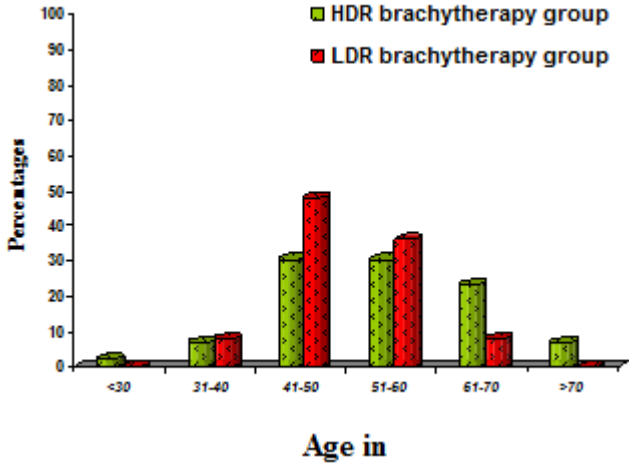
Significant figures
+ Suggestive significance (P value: 0.05<P<0.10)
* Moderately significant (P value:0.01<P ≤ 0.05)
** Strongly significant (P value : P≤0.01)
Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, Med Calc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

5. Results

The following were the results of the 43 patients and 25 patients treated with HDR brachytherapy and LDR brachytherapy respectively in the postoperative adjuvant setting with or without external beam irradiation.

The age distribution of patients studied in both the groups were as follows:

Age in years	HDR brachytherapy group	LDR brachytherapy group	Total
<30	1(2.3%)	0(0%)	1(1.5%)
31-40	3(7%)	2(8%)	5(7.4%)
41-50	13(30.2%)	12(48%)	25(36.8%)
51-60	13(30.2%)	9(36%)	22(32.4%)
61-70	10(23.3%)	2(8%)	12(17.6%)
>70	3(7%)	0(0%)	3(4.4%)
Total	43(100%)	25(100%)	68(100%)
Mean ±SD	55.67±11.58	50.44±8.09	53.75±10.68



Samples are age matched with P=0.100

The distribution of patients based on stage and grade were as follows:

FIGO Stage	*HDR brachytherapy group*	*LDR brachytherapy group*	*Total*
IbG1	5(11.6%)	1(4%)	6(8.8%)
IbG2	6(14%)	3(12%)	9(13.2%)
IbG3	3(7%)	1(4%)	4(5.9%)
IcG2	10(23.3%)	6(24.0%)	16(23.5%)
IcG3	6(14%)	4(16%)	10(14.7%)
IIG1	1(2.3%)	0(0%)	1(1.5%)
IIG2	1(2.3%)	3(12%)	4(5.9%)
IIG3	5(11.6%)	4(16%)	9(13.2%)
IIIG2	4(9.3%)	2(8%)	6(8.8%)
IIIG3	2(4.7%)	1(4%)	3(4.4%)
Total	43(100%)	25(100%)	68(100%)

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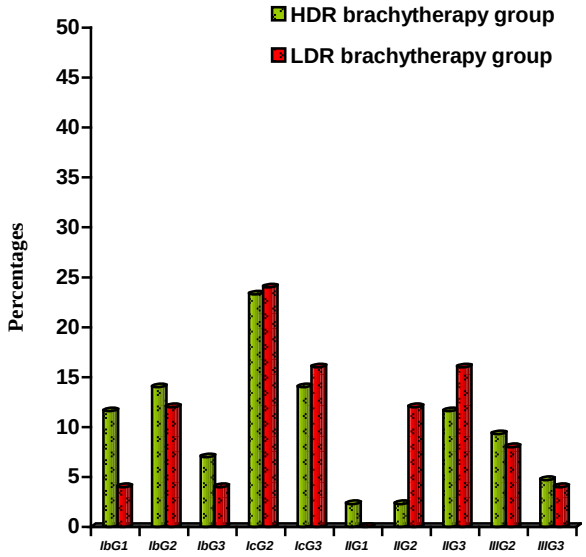
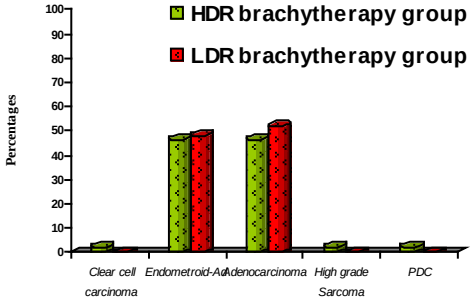


FIGO

The distribution of patients with respect to the histology are as follows:

HPR	*HDR brachytherapy group*	*LDR brachytherapy group*	*Total*
Clear cell carcinoma	1(2.3%)	0(0%)	1(1.5%)
Endometroid-Adenocarcinoma	20(46.5%)	12(48%)	32(47.1%)
Adenocarcinoma	20(46.5%)	13(52%)	33(48.5%)
High grade Sarcoma	1(2.3%)	0(0%)	1(1.5%)
PDC	1(2.3%)	0(0%)	1(1.5%)
Total	43(100%)	25(100%)	68(100%)



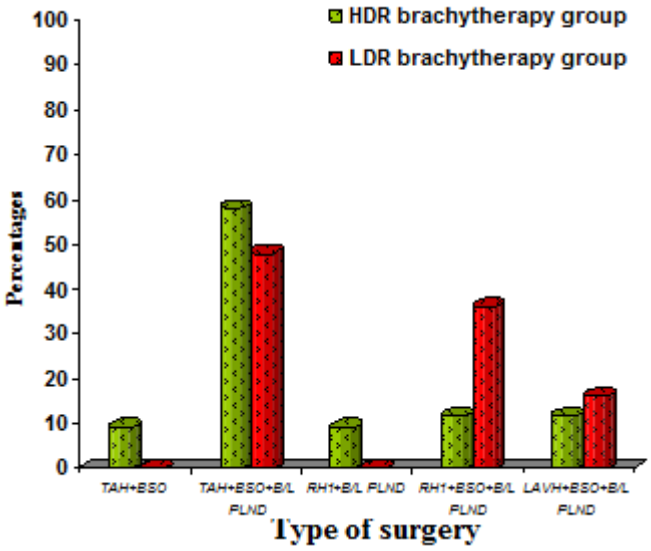
HPR

HPR findings are statistically similar in two groups with P=1.000

Grade of the tumour	HDR brachytherapy group	LDR brachytherapy group	Total
Grade I	6(14%)	0(0%)	6(8.8%)
Grade II	21(48.8%)	13(52%)	34(50%)
Grade III	16(37.2%)	12(48%)	28(41.2%)
Total	43(100%)	25(100%)	68(100%)

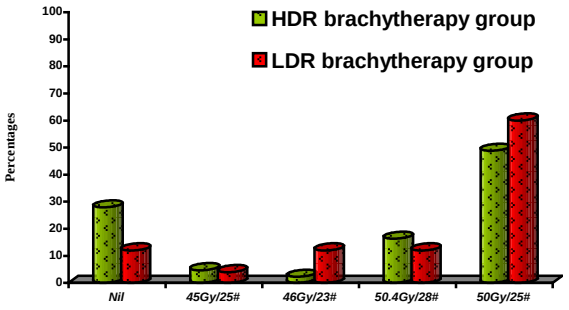
The type of surgery performed in both the groups are:

Type of surgery	*HDR brachytherapy group (n=43)*	*LDR brachytherapy group (n=25)*	*Total (n=68)*
TAH+BSO	4(9.3%)	0(0%)	4(5.9%)
TAH+BSO+B/L PLND	25(58.1%)	12(48%)	37(54.4%)
RH1+B/L PLND	4(9.3%)	0(0%)	4(5.9%)
RH1+BSO+B/L PLND	5(11.6%)	9(36%)	14(20.6%)
LAVH+BSO+B/L PLND	5(11.6%)	4(16%)	9(13.2%)



The teletherapy dose received by the remaining patients are as follows:

Teletherapy	*HDR brachytherapy group*	*LDR brachytherapy group*	*Total*
Nil	12(27.9%)	3(12%)	15(22.1%)
45Gy/25#	2(4.7%)	1(4%)	3(4.4%)
46Gy/23#	1(2.3%)	3(12%)	4(5.9%)
50.4Gy/28#	7(16.3%)	3(12%)	10(14.7%)
50Gy/25#	21(48.8%)	15(60%)	36(52.9%)
Total	43(100%)	25(100%)	68(100%)



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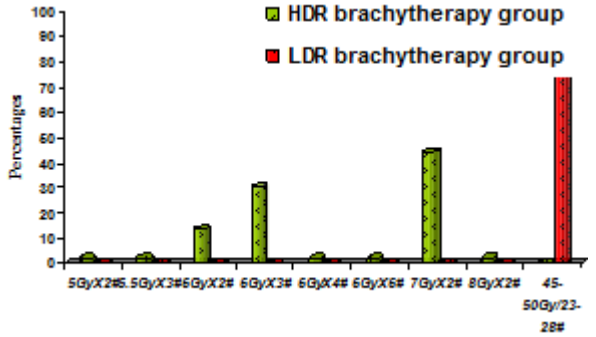
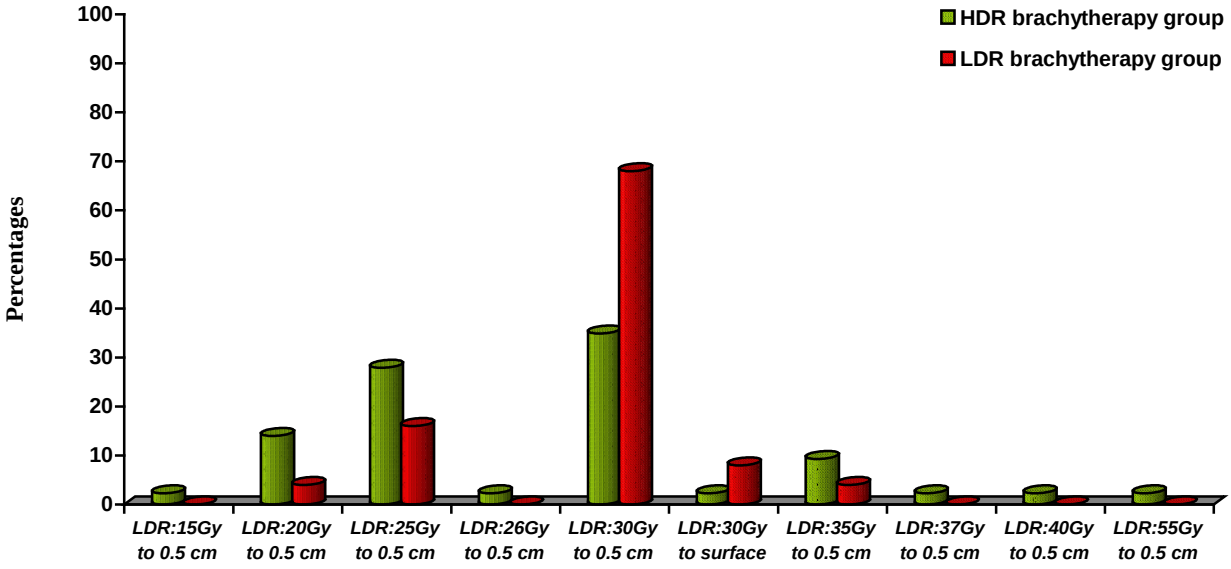
The brachytherapy doses received by the patients were as follows:

Brachytherapy	*HDR group (n=43)*	*LDR group (n=25)*	*Total (n=68)*
5GyX2#	1(2.3%)	0(0%)	1(1.5%)
5.5GyX3#	1(2.3%)	0(0%)	1(1.5%)
6GyX2#	6(14%)	0(0%)	6(8.8%)
6GyX3#	13(30.2%)	0(0%)	13(19.1%)
6GyX4#	1(2.3%)	0(0%)	1(1.5%)
6GyX6#	1(2.3%)	0(0%)	1(1.5%)
7GyX2#	19(44.2%)	0(0%)	19(27.9%)
8GyX2#	1(2.3%)	0(0%)	1(1.5%)
45-50Gy/23-28#	0(0%)	22(88%)	22(32.4%)

LDR - Eq Dose in Gy

LDR - Eq Dose in Gy	*HDR brachytherapy group*	*LDR brachytherapy group*	*Total*
LDR:15Gy to 0.5 cm	1(2.3%)	0(0%)	1(1.5%)
LDR:20Gy to 0.5 cm	6(14%)	1(4%)	7(10.3%)
LDR:25Gy to 0.5 cm	12(27.9%)	4(16%)	16(23.5%)
LDR:26Gy to 0.5 cm	1(2.3%)	0(0%)	1(1.5%)
LDR:30Gy to 0.5 cm	15(34.9%)	17(68%)	32(47.1%)
LDR:30Gy to surface	1(2.3%)	2(8%)	3(4.4%)
LDR:35Gy to 0.5 cm	4(9.3%)	1(4%)	5(7.4%)
LDR:37Gy to 0.5 cm	1(2.3%)	0(0%)	1(1.5%)
LDR:40Gy to 0.5 cm	1(2.3%)	0(0%)	1(1.5%)
LDR:55Gy to 0.5 cm	1(2.3%)	0(0%)	1(1.5%)
Total	43(100%)	25(100%)	68(100%)





LDR - Eq Dose in Gy

Chemotherapy

Chemotherapy	HDR group	LDR group	Total
Nil	39(90.7%)	25(100%)	64(94.1%)
Pacli+Carbo 3Cy	4(9.3%)	0(0%)	4(5.9%)
Total	43(100%)	25(100%)	68(100%)

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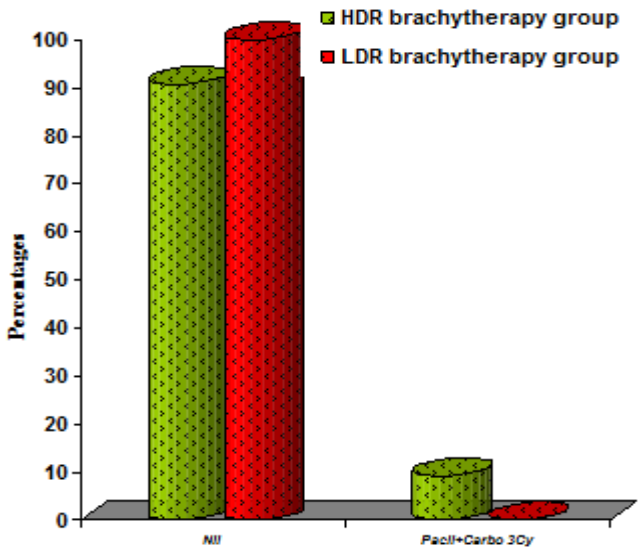


Follow up status

Follow up status	HDR brachytherapy group	LDR brachytherapy group	Total
No evidence of disease	33(76.7%)	22(88%)	55(80.9%)
Partial response	1(2.3%)	0(0%)	1(1.5%)
Lost to follow up	9(20.9%)	3(12%)	12(17.6%)
Total	43(100%)	25(100%)	68(100%)

Follow up status is statistically similar in two groups with P=0.462

Follow up days

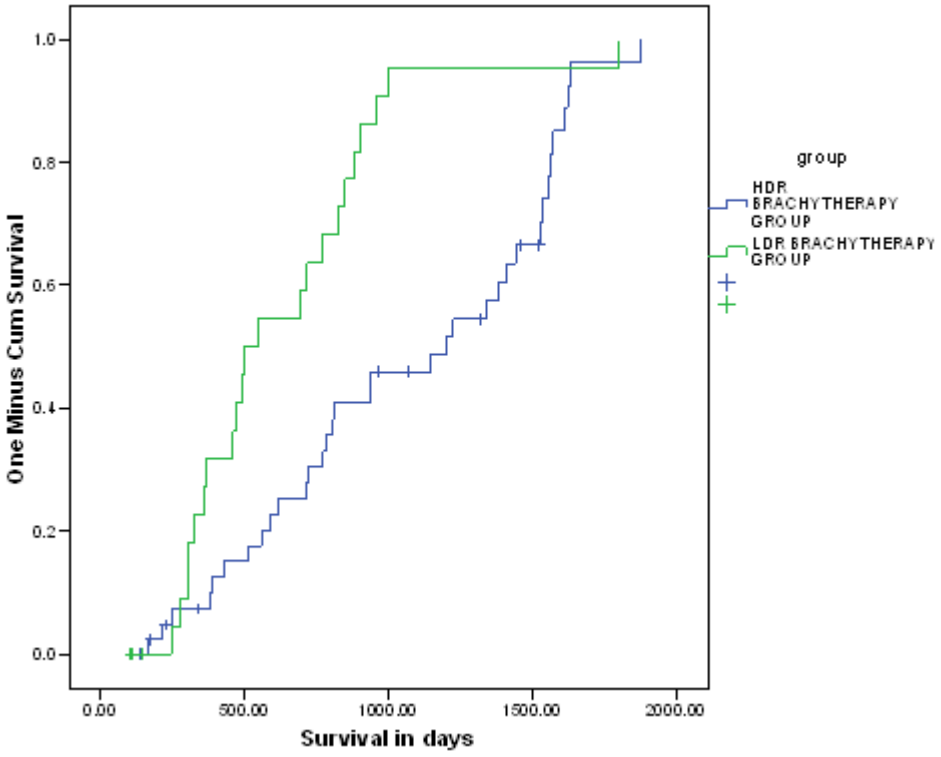
Follow up days	HDR brachytherapy group	LDR brachytherapy group	Total
<300	6(14%)	5(20%)	11(16.2%)
301-600	7(16.3%)	10(40%)	17(25%)
601-900	7(16.3%)	6(24%)	13(19.1%)
901-1200	5(11.6%)	3(12%)	8(11.8%)
1201-1500	8(18.6%)	0(0%)	8(11.8%)
>1500	10(23.3%)	1(4%)	11(16.2%)
Total	43(100%)	25(100%)	68(100%)
Mean ± SD	962.44±517.37	574.68±376.01	819.88±503.90

P=0.002**

Kaplan Meier Function analysis for predicting the survival after first diagnosis

Survival days	HDR brachytherapy group	LDR brachytherapy group	Total
Mean Survival in days	1078.93	637.05	920.62
Median Survival in days	1201	496	807
SE	80.72	76.15	64.52

Log rank test: $\chi 2=10.330$; P=0.001**



6. Discussion

Brachytherapy is an integral part of the treatment in the adjuvant setting of carcinoma of the endometrium. There has been a paradigm shift of brachytherapy delivery from low dose rate (LDR) to high dose rate(HDR) brachytherapy in view of patient convenience and reducing the risk of radiation exposure to the hospital personnel.

The dose fractionation and the techniques of delivering brachytherapy vary with institution and there have not been many studies comparing the HDR and the LDR brachytherapy groups.

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Postoperative pelvic radiotherapy (RT) is considered if risk factors are present, that is, deep myometrial invasion (50% or more of the myometrial width) and/or grade 2 or 3 histology. Patients with stage I endometrial carcinoma, treated with TAH–BSO followed by postoperative RT have a 5–year overall survival of 80–90%, a 5–year cancer specific survival of 90–95% and a 5-year locoregional recurrence rate of 4–8%[1-7]. The subgroup of patients with grade 3 tumors with deep (≥50%) myometrial invasion, however, have a considerably higher risk of locoregional and most notably, distant relapse [1,2,8,9].

In the randomised study reported by Aalders *et al*[1], 540 women who had undergone TAH–BSO and postoperative vaginal RT (60 Gy) were randomly assigned to additional pelvic RT or observation. Although pelvic RT reduced vaginal and pelvic recurrence rates (2% versus 7% in the control group), more distant metastases were found in the pelvic RT group (10% versus 5%), and survival was not improved (89% versus 91% 5–year survival). Only the subgroup with grade 3 tumors with deep (≥50%) invasion showed both improved local control and survival after additional pelvic RT. Most loco regional relapses are located in the vagina, mainly in the vaginal vault. In previously unirradiated patients reported salvage rates for isolated vaginal relapse are 40–80% [6,10-15]. The salvage rate of extravaginal pelvic relapse is low, ranging from <5% for patients who have received previous pelvic RT, to 20–30% in those not previously irradiated[6,11,12,15,16].

In the GOG staging study [17], the risk of pelvic node metastases in surgical stage I endometrial carcinoma was shown to be less than 10%, except for the subgroup with grade 3 tumors with deep (outer 33%) myometrial invasion, in which the risk amounted to 18%.

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