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RESEARCH ARTICLE

Comparative MRI evaluation of carcinoma cervix with and without dynamic contrast enhanced study and its implication in the therapeutic decision making

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ABSTRACT

Background: Cervical Cancer is the one of the major causes of cancer mortality which accounts for 17% of all cancer deaths among women aged between 30 and 69 years. The International Federation of Gynecology & Obstetrics (FIGO) staging system is widely used for clinical staging. The most important issue in staging of cervical cancer is to detect and identify early disease and magnetic resonance imaging (MRI) is the best single imaging investigation that can accurately determine tumour location, tumour size, depth of stromal invasion and extension into the lower uterine segment and status of locoregional lymph nodes. **Objectives:** Objectives of this study were to precise and better evaluation of patients with cervical cancer in pretreatment workup, as well as to determine sensitivity & specificity of noncontrast and dynamic contrast enhanced MRI for each predefined parameter those are helpful for FIGO staging. **Methods:** After obtaining clearance from the institutional ethical committee this randomized prospective comparative study was conducted including total of 50 eligible patients with predefined age group & clinically or biopsy proven cervical cancer with the aim to determine if noncontrast or dynamic contrast enhanced magnetic resonance imaging is better for pretreatment evaluation and appropriate FIGO staging of patients with carcinoma cervix. **Results:** Data were collected under multiple parameters like tumour size, depth of stromal invasion, vaginal spread, parametrial invasion and extent, involvement of ureter, involvement of pelvic and para aortic lymph nodes with size and distal metastasis. In our study, parametrial invasion was accurately assessed in 56% cases. Dynamic post contrast MRI detected stromal invasion in 24% cases when the depth of invasion varied between 5 – 20 mm and in 32% cases when the depth of invasion was more than 40 mm. The tumours measuring >5mm - <2cm sized tumours are better appreciated by DCEMRI which can be missed by NCMRI. **Conclusion:** This study has shown that there was a significant difference in radiologic staging of the disease using MRI with and without dynamic contrast enhanced (DCE) MRI. Use of MRI in staging improved the evaluation of parametrium and lymph nodal status thereby helping in the therapeutic decision making. Hence, there is a requirement of routine use of DCE MRI in pretreatment evaluation of carcinoma cervix.

Keywords: Carcinoma cervix, magnetic resonance imaging (MRI), parametrium, lateral pelvic wall.

Cervical cancer is the 4th most common malignancy among women in the world. It is preceded only by breast, colorectal and lung carcinoma in incidence. In India, it accounts for 6 - 29% of all cancers in women. It is accounting for 17% of all cancer deaths (a leading cause of mortality) among women aged between 30 and 69 years. It is estimated that cervical cancer affects approximately 1 in 53 Indian women during their lifetime. It has been diagnosed in younger women with average age of 45 years. Life time risk of cervical cancer is 2.4% in India [1].

The International Federation of Gynecology & Obstetrics (FIGO) staging system is widely used for clinical staging. In

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2018 the staging system was revised by the FIGO gynecologic oncology committee to allow imaging and pathological findings, where available, to assign the stage specifically for stage IIIC where involvement of pelvic & para aortic lymph nodes must be specified by adding notation of "r" (for radiology) and 'p' (for pathology). The new staging system is useful to distinguish survival groups. Stage IB1 and stage IB2 disease have distinct characteristics and survival outcome. Stage IIIC1 has superior survival rate compared to stage IIIA-B disease [2].

The most important issue in staging of cervical cancer is to detect and identify early disease from advanced one because the former can be treated with surgery only, whereas the latter must be treated either with radiation alone or radiation combined with chemotherapy. MRI is the best single imaging investigation that can accurately determine tumour location, tumour size, depth of stromal invasion & extension into the lower uterine segment and status of locoregional lymph nodes [3].

Aims and objectives: The aim of this study was to determine if noncontrast or dynamic contrast enhanced magnetic resonance imaging is better for pre-treatment evaluation and appropriate FIGO staging of patients with carcinoma cervix. Objectives of this study were to correct and better evaluation of patients in pretreatment workup, as well as to determine sensitivity and specificity of noncontrast and dynamic contrast enhanced MRI for each predefined parameter those are helpful for FIGO staging.

Methods

After obtaining clearance from the institutional ethical committee this randomized prospective comparative study was conducted in the Department of Radiodiagnosis of a tertiary care hospital between January 2019 and June 2020. A total of 50 eligible patientswith predefined age group and clinically or biopsy proven cervical cancer (at least 2 weeks post biopsy), coming to the department of Radiology for radiological evaluation were included in the study after obtaining informed written consent. Patients with previous medical surgical and radiation treatment for invasive cancer, patients with previous hysterectomy, patient having non-MRI compatible implant(s), cardiac pacemaker device or other contraindications to MRI were excluded from the study.

Non-contrast followed by dynamic contrast enhanced MRI on Siemens Magnetom 1 tesla MRI machine was performed on all patients. The imaging findings were interpreted and analyzed. Finally, the accuracy, sensitivity and specificity of MRI study was evaluated for correct FIGO staging and therapeutic decision. The patients were instructed to remain fasting for at least four hours prior to the examination to minimize the artifacts resulting from small bowl peristalsis. Axial T1 weighted images were acquired from the domes of diaphragm superiorly to the perineum inferiorly using 256 x 256 matrix, 32cm of field of view (FOV), 4 mm slice thickness and 1mm interslice gap which is optimum for evaluation lymphadenopathy in pelvis. High resolution T2 weighted images of the pelvis were acquired in axial, sagittal and coronal plane using 512 x 512 matrix, 24cm FOV, 4mm slice thickness and 1mm inter slice gap. This permits accurate assessment of tumor extension to the body of uterus, vagina, parametrium, rectum and urinary bladder. Fat suppressed sequences (STIR) were used to evaluate parametrial involvement. Dynamic images were obtained 45-60 seconds after intravenous injection of gadolinium chelate as these are helpful for the assessment of small tumor that are not readily identifiable on T2 weighted images but shows early contrast enhancement relative to the normal cervical stroma.

Following parameters were assessed - Tumour size, depth of stromal invasion, vaginal spread, parametrial invasion and extent, involvement of ureter, involvement of pelvic and para-aortic lymph nodes with size and distal metastasis.

Data were collected as per data collection protocol and analyzed with the assistance of a statistician. The results were depicted by graph, pie chart and bar diagrams. Categorical variables were expressed as number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test for Independence of Attributes/ Fisher's Exact Test as appropriate. The statistical software SPSS version 20 has been used for the analysis. An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it has been considered as significant.

Results

A total of 50 patients were included in our study, we found that majority of the patients were 56-60 years old (26%), 10% of the cases were below 50 years of age and 20% were above 65 years of age with a mean age of 59 years. The data for the clinical staging was taken from the 50 patients suspected of CA cervix by our clinician and staged during their first visit (table 1).

Parametrial involvement was seen in 28 cases out of 50 i.e. 56 % which was detected by clinical FIGO staging in only 16 cases (32%) and 18 cases (36%) on NC MRI (table

2). The difference between DCE MRI and clinical FIGO staging was found to be significant (p value <0.05).

In our study, we found 24 % of the cases showed a depth of stromal invasion between 5 mm and 2 cm on DCE MRI. Only 18% cases in this category were detected by NC MRI and 20 % on clinical assessment FIGO staging. However, this difference was not found to be significant. A majority of the cases (44%) had the greatest dimension between 2-4 cm which were correspondingly 50% on NC MRI and 48% on clinical FIGO staging (figure 1). The difference was not found to be significant.

For cases with lesions larger than 4 cm in size, the discrepancy between the three categories was again not significant i.e. 32 % on both NC MRI & DCE MRI and 30 % on clinical FIGO staging.

Both NC MRI and DCE MRI were able to detect 28 percent of the cases i.e. in 14 cases with pelvic lymph node involvement and hence showed no difference. Majority of the cases i.e. 36 cases (72%) did not show any enlarged pelvic nodes in our study (table 3). Clinical FIGO staging was not used in the assessment of this parameter.

Similar to the pelvic lymph node involvement, both NC MRI & DCE MRI were able to detect equal number of cases with para-aortic lymph node involvement i.e. 08 % (4 cases out of 50) and showed no difference. Clinical FIGO staging could not be assessed in this category.

Involvement of the upper 2/3rd of vagina was seen in 2 cases out of 50 on NC MRI (4%), 6 cases on CE MRI and 6 cases out of 50 in FIGO.

Involvement of the lower 1/3rd along with upper 2/3rd of vagina was detected in 13 cases out of 50 on NC MRI (16%) as well as on DCE MRI, however it was detected in 14 cases out of 50 in clinical FIGO assessment (figure 2). However, the difference between the three modalities was not found to be significant with p value of 0.596.

Involvement of the lateral pelvic wall was seen in 9 cases out of 50 i.e. 18 % of the cases in DCE MRI was able to detect the maximum number of cases. At the same time, both NC MRI and clinical FIGO staging was able to detect only 14% of the cases. However, the difference between the three modalities to assess the lateral pelvic wall involvement was not found to be significant (p value 0.814) (table 4). The involvement of the ureter was seen in 4 cases out of 50 in both NC MRI and DCE MRI i.e. 8 % of the cases and showed no difference in the NC MRI and DCE MRI in assessment of this factor Clinical FIGO staging could not be used in detection of the involvement of the ureter (table 5).

Involvement of the urinary bladder was seen in 8 cases out of 50 on DCE MRI (16%) and only in 6 cases on NC MRI (figure 3). Only 2 cases of urinary bladder involvement were detected in clinical FIGO staging in the form of fistula formation. However, the difference between the three modalities was not found to be significant.

Table 1: Clinical FIGO staging of carcinoma cervix

Staging	Substaging	No of patients	Percentage
I	1B1	4	8
	IB2	8	16
II	IIA1	14	28
	IIB	10	20
	IIA2	0	0
III	IIIA	7	14
	IIIB	1	2
IV	IVA	6	12
	IVB	0	0
Total		50	100

Table 2: Comparative analysis of parametrial involvement in NCMRI, CEMRI and clinical FIGO staging

Parameters		Group N (%)			Total	P	Significance
		NCMRI	CEMRI	FIGO	N (%)	Value	
Parametrial involvement	Absent	32(64)	22(44)	34(68)	88(58.67)	0.033	Significant
	Present	18(36)	28(56)	16(32)	62(41.33)		
Total		50(100)	50(100)	50(100)	150(100)		

Pearson's chi square test were used for independence of attributes

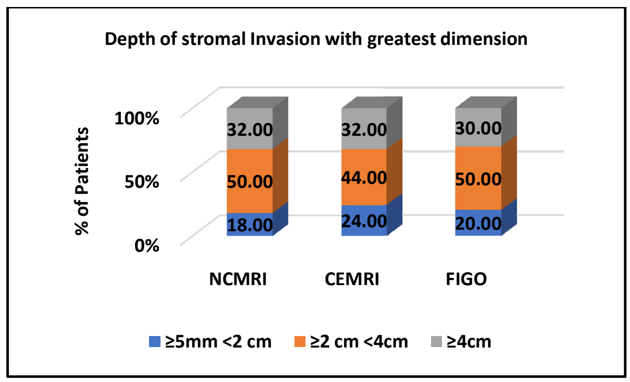

Figure 1: Depth of stromal invasion with greatest dimension

Table 3: Comparative analysis of pelvic lymph node involvement in NCMRI, CEMRI and clinical FIGO staging

Parameters		Group N(%)		Total	P -	Significance
		NCMRI	CEMRI	N(%)	Value	
Pelvic lymph node involvement	No involvement	36(72)	36(72)	72(72)	1.000	Not Significant
	Involvement	14(28)	14(28)	28(28)		
Total		50(100)	50(100)	100(100)		

Pearson's chi square test were used for independence of attributes

Table 4: Comparative analysis of lateral pelvic wall involvement in NCMRI, CEMRI and clinical FIGO staging

Parameters		Group N (%) NCMRI	CEMRI	FIGO	Total N (%)	P - value	Significance
Lateral pelvic wall involvement	Absent	43(86)	41(82)	43(86)	127(84.67)	0.814	Not Significant
	Present	7(14)	9(18)	7(14)	23(15.33)		
Total		50(100)	50(100)	50(100)	150(100)		

Pearson's chi square test was used for independence of attributes.

Table 5: Comparative analysis of Ureter involvement in NCMRI, CEMRI and clinical FIGO staging

Parameters		Group N(%) NCMRI	CEMRI	FIGO	Total N(%)	P - Value	Significance
Ureter involvement	Absent	46(92)	46(92)	50(100)	142(94.67)	0.121	Not Significant
	Present	4(8)	4(8)	0(0)	8(5.33)		
Total		50(100)	50(100)	50(100)	150(100)		

Fisher's exact test were used for the analysis

Involvement of the rectum was seen in 6 cases out of 50 on DCE MRI and 8 cases in NC MRI (figure 3). At the same time, 5 cases were detected on clinical FIGO staging. Again, the difference was not found to be significant with p value of 0.278 which is statistically not significant. Liver metastasis was seen in 3 cases out of 50 cases in both NC MRI & CE MRI. Bone metastasis was seen in 1 case out of 50 in CE MRI, however it was not detected in NC MRI. Clinical FIGO staging could not be used in detection of distant metastasis. Comparative analysis of all three modalities of NCMRI, DCE MRI and clinical FIGO was done using Fisher's exact test (table 6) and calculated the statistically significant p value of 0.046 (p value < 0.05).

Table 6: Comparative analysis of staging (FIGO staging) of CA cervix with NCMRI, CEMRI and clinical FIGO staging

Parameters		Group N(%) NCMRI	CEMRI	FIGO	Total N(%)	P - Value	Significance
Stage	1B2	0(0)	0(0)	1(2)	1(0.67)	0.046	Significant
	2A1	0(0)	0(0)	1(2)	1(0.67)		
	2B	3(6)	7(14)	1(2)	11(7.33)		
	3A	0(0)	0(0)	1(2)	1(0.67)		
	IB1	9(18)	9(18)	10(20)	28(18.67)		
	IB2	22(44)	19(38)	21(42)	62(41.33)		
	IB3	1(2)	0(0)	0(0)	1(0.67)		
	IIB	0(0)	0(0)	1(2)	1(0.67)		
	IIIA	0(0)	0(0)	6(12)	6(4)		
	IIIB	0(0)	0(0)	1(2)	1(0.67)		
	IIIC1	1(2)	1(2)	0(0)	2(1.33)		
	IVA	11(22)	11(22)	7(14)	29(19.33)		
	IVB	3(6)	3(6)	0(0)	6(4)		
Total		50(100)	50(100)	50(100)	150(100)		

Fisher's exact test were used for the analysis

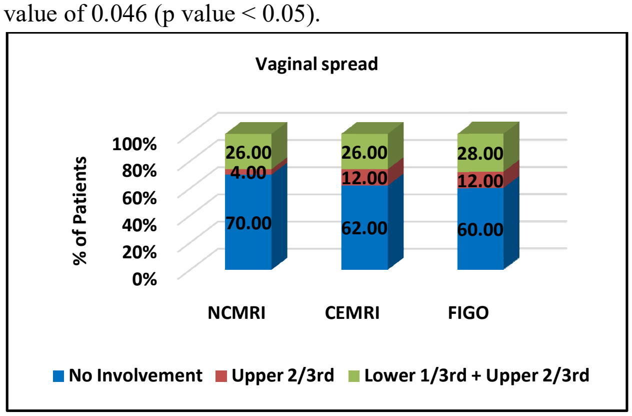

Figure 2: Vaginal spread in NCMRI, CEMRI and clinical FIGO staging

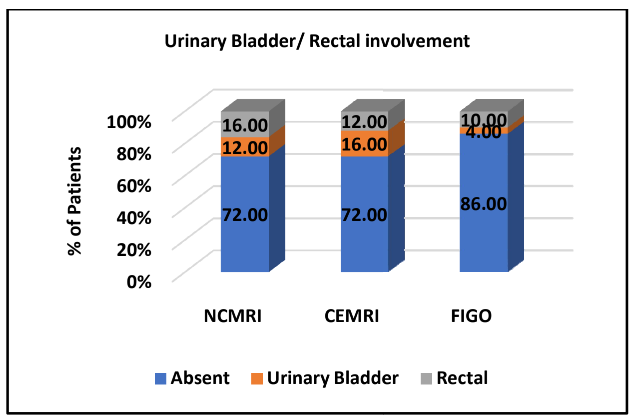

Figure 3: Urinary bladder/rectal involvement in NCMRI, CEMRI and clinical FIGO staging

Discussion

Worldwide, cancer of the cervix is the fourth commonest malignancy afflicting women especially of the lower socioeconomic status [4, 5]. Although carcinoma cervix has two age peaks, it is most often detected in women between 30 to 50 years age [5, 6]. In our study majority of the patients were

56-60 years old (26%), 10% of the cases were below 50 years of age and 20% were above 65 years of age with a mean age of 59 years. Multiparity, multiple sexual partners, genital infections and married for a long duration are some of the known factors predisposing to cancer cervix. In our study, 38 cases out of 50 were multiparous.

Although several radiological imaging modalities are readily available for pretreatment work up of a case of carcinoma cervix, MRI is an extremely promising, worthy and reliable investigation [7, 8]. Acknowledging the reliable contribution of MRI, the current FIGO classification has included the imaging methods as an adjunct for staging carcinoma cervix. Even though MRI has no role to play in the evaluation of stage IA of cervical cancer, it is now recognized to be the preferred modality for imaging tumours higher than stage IB2 because it accurately assesses the extent of tumour invasion [9.10]. MRI is far superior than clinical staging for tumour location and size and improves the accuracy of FIGO staging to 96% [10, 11].

The standard MRI protocol in a case of cancer cervix includes T2 weighted imaging of the pelvis is different planes. The sections are acquired obliquely along the plane of cervical canal because this facilitates the correct and precise assessment of tumour margins and infiltration into the parametrium [9, 12]. Dynamic contrast enhanced MRI characterizes tumour microcirculation and it is a dynamic examination technique that displays alterations in signal intensity over time after intravenous administration of gadolinium chelate. MRI plays an extremely crucial role not merely in the estimation of the size of the tumor but more important in picking up parametrial invasion [11, 12]. This in turn, assists in choosing the correct treatment modality and protocol [13, 14]. In our study also, MRI was found to be sensitive in precise assessment parametrial invasion. Dynamic contrast enhanced MRI was found to be even more sensitive in identifying parametrial invasion as compared to noncontrast MRI in our study [13]. Although noncontrast MRI detected parametrial invasion in 18 cases, dynamic contrast enhanced MRI enhanced the detection to 28 cases. Clinically, only 16 patients were suspected to have parametrial invasion.

Noncontrast MRI has a sensitivity of 38 – 100% and a specificity of upto 92% in assessing parametrial infiltration. On T2 weighted images, signs indication parametrial invasion includes the discontinuity of the cervical margins, spicules infiltrating the parametrium and encasement of the adjacent vessels. If the hypointense ring around the cervix remains intact, it practically excludes parametrial invasion [9]. In our study, parametrial invasion was accurately assessed in 56% cases.

The depth of stromal invasion has important prognostic implications because deeply invasive cervical carcinoma is treated with radical hysterectomy. Therefore, preoperative evaluation of the degree of stromal invasion is important in planning treatment [15]. Stromal invasion on MRI is indicated by a high signal intensity area compared to the hypointense cervical stroma (normal healthy cervix) on T2 weighted MR images, an early focal enhancement in the cervix in the early phase of dynamic MR images and a cervical mass showing enhancement on contrast enhanced images [13,16]. In a path breaking study by Seki and colleagues in 1997, invasive carcinoma cervix displayed focal enhancement earlier than or simultaneously with the cervical epithelium [15]. The same was observed in our study also. Dynamic post contrast MRI detected stromal invasion in 24% cases when the depth of invasion varied between 5 – 20 mm and in 32% cases when the depth of invasion was more than 40 mm. The tumours measuring >5mm - <2cm sized tumours are better appreciated by DCEMRI which can be missed by NCMRI. Thus, early decision for modified radical/ radical trachelectomy on DCEMRI can be taken.

Even though lymph node status is not an inherent part of FIGO classification, metastases to the lymph nodes are independent adverse prognostic factors [17]. Size of the lymph node is used as a criterion for significance. If the mean short axis diameter is greater than 10 mm, the lymph node is regarded as suspicious. According to the literature MRI has a sensitivity of 37 – 90% and specificity of 71-100% in diagnosis of lymphadenopathy. In our study, significant lymphadenopathy was detected in 28% cases. The smaller number in our study is because majority of the cases were identified in the early stage 1B2.

For staging purposes, vaginal infiltration is categorized into upper two-third of the vagina and lower one third invasions. Invasion of the lower one-third of the vagina increases the stage from IIA to IIIA, which affects the strategy of radiation therapy. In our study, the upper two-thirds of the vagina was the most common site for extrauterine tumour invasion, with an incidence of 26%. This incidence was nearly similar to that of Chen and colleagues who reported that the overall incidence of vaginal invasion by cervical carcinoma was 34.2% [18].

Lateral spread to the lateral pelvic wall mandates radiologic evaluation of the ureters. The anatomic position of the ureter (within 2 cm of the uterine cervix) makes the ureter vulnerable to involvement. About one third of patients with stage IIIB cancers have ureteral obstruction and about 5% have bilateral obstruction. The obstruction usually occurs in the distal third of the ureter. In our study, ureter was involved in 8% cases. In our study, both the noncontrast and postcontrast MRI imaging findings were in agreement with each other in detecting rectal involvement. So, ureteric involvement, urinary bladder and rectal involvement, pelvic lymph node and para-aortic lymph node involvement, there is no significant difference in implication in the therapeutic decision making between NCMRI and DCEMRI.

Thus, the use of MRI in the staging of CA cervix improved the detection of vaginal and parametrial involvement, made assessment of tumour size more accurate, thus improving upon the earlier clinical staging which was done without input from imaging [19.20]. MRI also made it possible to evaluate lymph nodal involvement and incorporate it in the improved staging. MRI also provided additional inputs like involvement of ureters and viscera, thus providing valuable inputs for therapeutic decision making and disease prognostication [21,22].

After the assessment of the individual parameters on the different modalities, namely NC MRI, DCE MRI & clinical FIGO staging, it was found that in the assessment of the parametrial involvement that difference between DCE MRI and clinical FIGO staging was significant. Hence MRI evaluation in the staging made a difference predominantly in stage II B where the parametrial invasion was missed both by clinical staging and NC MRI in a significant number of cases. There were few parameters for example involvement of ureter, regional lymphadenopathy and distant metastases, in which clinical FIGO staging could not assess due to the absence of radiological investigations.

However, it was found that there was a significant difference in radiologic staging of the disease using MRI with and without DCE. Use of MRI in staging improved the evaluation of parametrium and lymph nodal status thereby helping in the therapeutic decision making. Comparative analysis of all three modalities of NCMRI, DCE MRI and clinical FIGO was done and it was statistically significant ($p = 0.046$). Hence, there is a requirement of DCE MRI in routine evaluation of Ca cervix for complete staging of carcinoma cervix patients with NCMRI and clinical FIGO staging

Conclusion

MRI is a noninvasive radiological modality for pretreatment evaluation of patients with suspected cervical malignancy, not only for detecting and characterizing the tumour itself, but also for accurate assessment of the tumor invasion in the parametrium. MRI is also capable of detecting significant locoregional lymphadenopathy, subsequent more precise tumor staging and planning the treatment strategies. Dynamic post contrast enhanced MRI is extremely useful in detecting stromal invasion more than 5 mm for cancer staging, which impacts prognosis.

This study has shown that there was a significant difference in radiologic staging of the disease using MRI with and without DCE. Use of MRI in staging improved the evaluation of parametrium and lymph nodal status thereby helping in the therapeutic decision making. Hence, there is a requirement of routine use of DCE MRI in pretreatment evaluation of Ca cervix. It was also found that DCE MRI is superior to NC MRI for evaluation of CA cervix for staging, prognostication and subsequent treatment planning especially in Stage IIB where the detection of parametrial invasion seemed better with DCE MRI. Though this study did not show a statistically significant advantage of DCE MRI, in the evaluation of other stages, this study is limited by small sample size and lack of follow up and histological correlation. Routine use of DCE MRI in larger studies are required for evaluating adequate numbers in all stages incorporating histological details of patients who have undergone surgery.

Conflict of interest: None. **Disclaimer:** Nil.

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