

Pelvic exenteration for locally advanced and recurrent rectal cancer: long-term outcomes and prognostic factors

Exenteración pélvica para cáncer de recto localmente avanzado y recurrente: resultados a largo plazo y factores pronósticos

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Abstract

Introduction: Pelvic exenteration is a radical treatment for locally advanced and recurrent pelvic tumors. The aim of this study was to analyze the perioperative and long-term outcomes of patients undergoing pelvic exenteration for rectal cancer at a referral center in Mexico City. **Method:** We included all patients who underwent pelvic exenteration due to rectal cancer between 1995 and 2019. Demographic, clinical, surgical and pathological variables were analyzed. **Results:** 18 patients were included (16 locally advanced and 2 recurrent). The male-female ratio was 1:3.5. The highest morbidity was 27.7%. Intraoperative bleeding ≥ 1000 ml was associated with postoperative morbidity (80 vs. 20%; $p = 0.029$) and mortality (100 vs. 0; $p = 0.043$). The median overall survival was 102 months. Overall survival and disease free survival at 5 years after exenteration were 44.4% and 38.8%, respectively. Lymphovascular invasion of the tumor was a poor prognostic factor for disease free survival ($p = 0.017$). **Conclusions:** Pelvic exenteration for rectal cancer is a surgical procedure with high morbidity and mortality. Lymphovascular invasion is a poor prognostic factor for disease-free survival.

Keywords: Pelvic exenteration. Rectal cancer. Lymphovascular invasion. CR-POSSUM.

Resumen

Objetivo: El objetivo de este trabajo fue analizar los resultados perioperatorios y a largo plazo de los pacientes sometidos a exenteración pélvica para cáncer de recto en un centro de referencia en la Ciudad de México. **Método:** Se incluyeron todos los pacientes que se sometieron a exenteración pélvica por cáncer de recto entre 1995 y 2019. Se analizaron variables demográficas, clínicas, quirúrgicas y patológicas. **Resultados:** Se incluyeron 18 pacientes operados por cáncer de recto (16 localmente avanzados y 2 recurrentes). La relación hombre: mujer fue de 1:3.5. La morbilidad mayor fue del 27.7%. El sangrado intraoperatorio ≥ 1000 ml se asoció con morbilidad (80 vs. 20%; $p = 0.029$) y mortalidad posoperatoria (100 vs. 0; $p = 0.043$). La mediana de supervivencia global fue 102 meses. Las supervivencias global y libre de enfermedad a los 5 años fueron del 44.4% y el 38.8%, respectivamente. La invasión linfovascular fue un factor de mal pronóstico para supervivencia libre de enfermedad ($p = 0.017$). **Conclusiones:** La exenteración pélvica para el cáncer de recto es un procedimiento quirúrgico con altas morbilidad y mortalidad. La invasión linfovascular es un factor de mal pronóstico para la supervivencia libre de enfermedad.

Palabras clave: Exenteración pélvica. Cáncer de recto. Invasión linfovascular. CR-POSSUM.

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Introduction

Pelvic exenteration is a radical surgical procedure for local and recurrent pelvic neoplasms. First described by Brunschwig in 1948¹, it was initially designed as a palliative procedure for the treatment of recurrent bladder tumors and other gynecologic cancers^{2,3}, but currently it is regarded as a potential curative treatment for locally-advanced rectal cancer. Around 10% of primary colorectal cancers have tumor invasion to adjacent organs⁴. Therefore, multiple organ resection can be offered in order to achieve negative surgical margins, which is the most important factor for long-term survival⁵.

Classically, total pelvic exenteration is defined as extirpation of the rectum, sigmoid colon, distal ureters, bladder, internal reproductive organs, surrounding lymph nodes, and pelvic peritoneum. In addition, resection of adjacent muscles, ligaments, and neurovascular or bone structures may be necessary.

Early recognition of relapses observed with radiotherapy and multidisciplinary care have increased quality of life and reduced the need for total pelvic exenteration⁶.

However, if the therapeutic strategy includes pelvic exenteration, morbidity and mortality should be considered, and patients must be properly selected⁷. In addition, postoperative results depend on the experience of the medical team⁸.

Over the past 60 years, significant medical advances have made pelvic exenteration and other procedures for rectal cancer much safer, as demonstrated by the trend towards a lower mortality rate⁹. The purpose of this study is to compare perioperative and long-term outcomes of pelvic exenteration for rectal cancer in a referral center of Mexico City.

Method

A retrospective analysis of all patients who underwent pelvic exenteration for rectal cancer was carried out in a referral center of Mexico City between 1995 and 2019. Rectal cancer diagnosis was established by histopathological examination. Patients with incomplete records or files were excluded. Demographic, clinical, histopathological, and surgical variables were collected. All patients underwent an extensive preoperative workup, which included computed tomography (CT) and magnetic resonance imaging (MRI), according to current guidelines.

To quantify the number of resected pelvic compartments we used the classification described by the Royal Marsden Hospital¹⁰. All patients were classified according to National Comprehensive Cancer Network (NCCN) guidelines, version 3.2019, for rectal cancer¹¹. Operative mortality was defined as that occurring within the first 90 days after surgery. Morbidity was rated according to the Clavien-Dindo classification, with the highest morbidity being Clavien-Dindo III-V¹².

The usefulness of the Colorectal Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (CR-POSSUM)¹³ as a mortality predictor was analyzed. The cutoff value was 10 points.

We used the observed-expected mortality ratio (OEMR) to predict patient mortality (observed mortality/calculated mortality). We also used a Charlson comorbidity index¹⁴ score ≥ 3 as a risk factor for morbidity and mortality. Histopathological evaluations were carried out by Institute-certified pathologists. Recurrence was diagnosed by direct biopsy or imaging. Local recurrence was defined as recurrence of disease within the pelvic cavity, and distant recurrence was defined as disease recurrence outside the pelvic cavity. Lymphovascular invasion was defined as the identification of tumor cells that spread to areas covered by endothelium. The study was approved by the Institutional Ethics Review Committee (SCI-1869-16/16-1).

Descriptive analysis of variables was based on the type of variable. Continuous variables were analyzed using a nonparametric test, and the chi-square test was used for categorical variables statistical contrast. Cumulative rates and influence of factors on survival were measured with the Kaplan-Meier method, using the log-rank test. A Cox proportional hazards model was also used to analyze factors associated with overall and disease-free survival. A p-value < 0.05 was regarded as significant.

No models were created for the multivariate analysis to evaluate independent variables, since the study group was too small for the parameters identified by univariate analysis. Statistical analysis was performed with SPSS, version 21.0 (SPSS, Chicago, IL, USA) for Windows.

Results

Between 1995 and 2019, 18 patients underwent pelvic exenteration for primary and recurrent rectal

cancer. Eight patients (44.4%) underwent surgery before 2010. The male: female ratio was 1:3.5. Median age was 60 years (range: 43-76). Median body mass index was 24.15 kg/m² (range: 16-48). Surgical indication was locally advanced rectal cancer in 16 patients (88.8%) and recurrent rectal cancer in 2 (11.2%). In those patients operated on for recurrent cancer, it was identified within a median time of 16 months after primary tumor resection surgery. Patient characteristics and perioperative variables are described in table 1.

The surgical procedure was posterior pelvic exenteration in 15 patients (83.3%) and anterior pelvic exenteration in 3 (16.6%). The number of resected pelvic compartments was similar in all procedures, since most patients underwent resection of four or more compartments according to the Royal Marsden Hospital classification. Perineal reconstruction with transverse rectus abdominis muscle was only performed in three cases (16.6%). In 16 patients (88.8%) was an R0 resection achieved.

Twelve patients (75%) received some type of neoadjuvant therapy and 8 (44.4%) received adjuvant therapy. According to the degree of differentiation, 14 cases (77.7%) were moderately-differentiated, 2 (11.1%) were well-differentiated, and other 2 (11.1%) were poorly-differentiated rectal adenocarcinoma.

Overall complication rate was 61.1%, with a morbidity higher than 27.7% (Clavien-Dindo III-IV). These complications were more common in those procedures performed before 2010 (40 vs. 60%). Most complications were conservatively managed. Only 3 patients (16.6%) required surgical intervention that included abscess/abdominal collection drainage. The profile of postoperative complications is described in table 2. We found a higher major morbidity rate in patients with an American Society of Anesthesiologists (ASA) score ≥ 3 (100 vs. 0%; $p = 0.047$). Intraoperative bleeding ≥ 1000 mL was also significantly related to major morbidity (80% vs. 20%; $p = 0.029$) (Table 3).

Three patients (16.6%) died within 90 days after surgery. The causes were abdominal sepsis with multiple organ failure in one patient and hospital-acquired pneumonia in the other two. There was no relationship between postoperative mortality and the year the procedure was performed at. We noted that patients with intraoperative bleeding ≥ 1000 mL were also associated with higher postoperative mortality (100 vs. 0%; $p = 0.043$) (Table 3).

Table 1. Patient clinical characteristics. Variables are expressed as medians (range) or number (%)

General	n (%)
Age, years	60 (43-76)
Female gender	14 (77.8)
Charlson ≥ 3	6 (33.3)
ASA ≥ 3	10 (55.5)
BMI	24.15 (16-31)
Neoadjuvant treatment	12 (75)
Intraoperative bleeding (mL)	700 (200-6500)
Surgery duration (min)	415 (264-600)
Resected compartments	
2	2 (11.1)
3	4 (22.2)
4	8 (44.4)
5	4 (22.2)
Flap construction	3 (16.6)
Negative surgical margins	16 (88.8)
Stage	
I	2 (11.1)
II	9 (50)
III	4 (22.2)
IV	3 (16.7)
Postoperative complication	11 (61.1)
Clavien-Dindo	
II	4
III	2
IV	1
V	2
Hospital stay (days)	10 (7-42)
Adjuvant therapy	8 (44.4)
Surgery date	
After 2010	10 (55.5)
Up to 2010	8 (44.4)

ASA: American Society of Anesthesiologists; BMI: body mass index.

Regarding the CR-POSSUM score, 5 patients (27.7%) had > 10 points. CR-POSSUM-predicted mortality and observed mortality were 9.6% and 16.6%, respectively ($p = 0.059$). Table 3 describes in detail the univariate analysis of factors associated with postoperative morbidity and mortality.

Follow-up and survival

During a median follow-up of 38 months (range: 10-66), 4 patients (22.2%) died, one due to cancer

Table 2. Complications after pelvic exenteration

General	n (%)
Pelvic collection or abscess	4 (22.2)
Wound dehiscence	2 (11.1)
Ileus or small bowel obstruction	3 (16.6)
Late postoperative bleeding	3 (16.6)
Urinary tract injury or infection	1 (0.5)
Pneumonia	2 (11.1)
Other (acute renal failure, acute myocardial infarction)	2 (11.1)

progression and three for non-oncological reasons (pneumonia, leukemia, and cerebrovascular disease).

Median overall survival for the entire cohort was 102 months (range: 3-166). This median overall survival was lower for those patients operated before 2010 (51.2 vs. 76.9 months). Overall recurrence rate was 33.3%, with an average recurrence time of 24.5 months (range: 5-54), with 40% of locoregional relapse and 60% of distant relapse. Only one patient had local and distant recurrence. By the end of the study, four patients had metastatic disease (three to the liver and one to the adrenal gland). Overall survival (OS) and 5-year disease-free survival (DFS) for the entire cohort were 44.4% and 38.8%, respectively (Fig. 1).

Prognostic factors for overall survival and disease-free survival

The univariate analysis demonstrated two statistically significant poor prognostic factors for survival. Lymphovascular invasion, which was present in 5 patients (55.5%), had statistical significance for DFS ($p = 0.017$), and perineural invasion, which was present in 4 patients (22.2%), showed a trend toward statistical significance ($p = 0.064$). These results were not consistent for OS (Fig. 2).

On the other hand, we found that the female gender was associated with poor OS prognosis ($p = 0.031$). Clinical stage, surgical margins, lymph nodes, metastatic disease, use of adjuvant or neoadjuvant therapy, and the year the procedure was performed had no significant impact on survival prognosis (Table 4).

Table 3. Univariate analysis of factors associated with postoperative major morbidity and mortality (at 90 days)

Variables	Morbidity		Mortality	
	Yes (n = 5) %	No (n = 13) %	Yes (n = 3) %	No (n = 15) %
Age				
≥ 60 years	3 (60)	6 (46.2)	2 (66.6)	7 (46.6)
< 60 years	2 (40)	7 (53.8)	1 (33.3)	8 (53.4)
			0.500	0.500
Gender				
Females	3 (60)	11 (84.6)	1 (33.3)	2 (13.4)
Males	2 (40)	2 (15.4)	2 (66.6)	13 (86.6)
			0.533	0.108
Charlson				
≥ 3	2 (40)	4 (30.8)	1 (33.3)	5 (33.4)
< 3	3 (60)	9 (69.2)	2 (66.6)	10 (66.6)
			0.385	0.755
ASA				
≥ 3	5 (100)	5 (38.5)	3 (100)	6 (40)
< 3	0	8 (61.5)	0	9 (60)
			0.036	0.216
BMI				
≥ 25	1 (20)	7 (53.8)	0	8 (53.4)
< 25	4 (80)	6 (46.15)	3 (100)	7 (46.6)
			0.314	0.216
Perioperative bleeding (mL)				
≥ 1,000	4 (80)	3 (23.1)	3 (100)	4 (26.6)
< 1,000	1 (20)	10 (76.9)	0	11 (73.4)
			0.047	0.043
Surgery duration (min)				
≥ 360	5 (100)	8 (61.5)	3 (100)	10 (66.6)
< 360	0	5 (38.5)	0	5 (33.4)
			0.701	0.554
Resected compartments				
> 3	4 (80)	9 (69.2)	2 (66.6)	10 (66.6)
< 3	1 (20)	4 (30.8)	1 (33.3)	5 (33.4)
			0.561	0.730
CR-POSSUM				
≥ 10	3 (60)	5 (38.5)	0 (33.3)	5 (33.4)
< 10	2 (40)	8 (61.5)	3 (100)	10 (66.6)
			0.608	0.059
Date of surgery				
After 2010	2 (40)	8 (61.5)	1 (33.3)	9 (60)
Up to 2010	3 (60)	5 (38.5)	2 (66.6)	6 (40)
			0.618	0.589

ASA: American Society of Anesthesiologists; BMI: body mass index; CR-POSSUM: Colorectal Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity.

Discussion

Pelvic exenteration was first described as a palliative procedure for gynecologic neoplasms, and was later described for locally-advanced and recurrent rectal cancer^{15,16}. Reported mortality in the first series was 30%, and there were no long-term survivors¹, but the most recent publications show that it has been

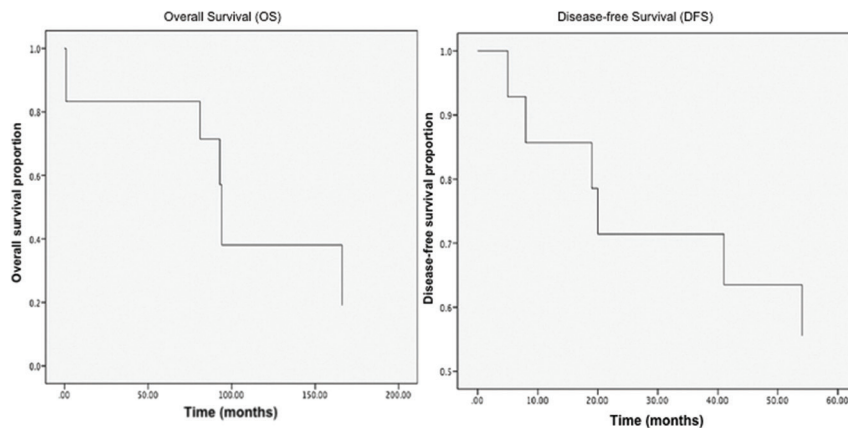


Figure 1. Kaplan-Meier 5-year overall survival and disease-free survival curves for the entire cohort.

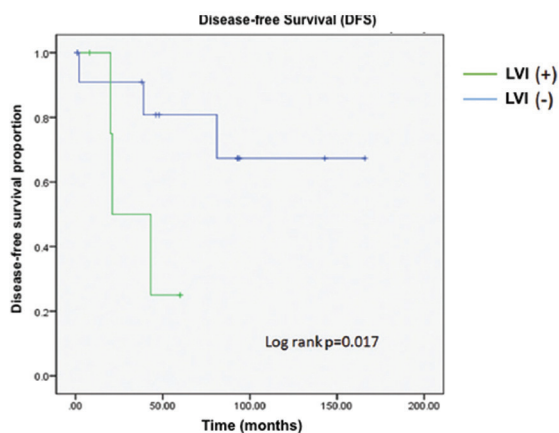


Figure 2. Kaplan-Meier disease-free survival curve according to the presence (green line) or absence (blue line) of tumor lymphovascular invasion. DFS: disease-free survival; LVI: lymphovascular invasion.

reduced from 0% to 10%¹⁷, which demonstrates an improvement in medical care standards. Perioperative mortality reported in this series is 16.6% (3 patients), which reflects that pelvic exenteration mortality shows an approximation to that of elective radical resection for primary colorectal cancer¹⁸.

Although not statistically significant, a value > 10 on CR-POSSUM score showed a statistical trend for 30-day mortality ($p = 0.059$). At this point, no other series has used the CR-POSSUM score in pelvic exenteration, since, generally, it is used for elective colorectal surgery with or without cancer^{19,20}. Cheung et al.²¹ explain that CR-POSSUM was developed to predict 30-day postoperative mortality in patients scheduled for colorectal surgery, and that its inability to predict survival could be due to the fact that it was not

designed to predict 30-day postsurgical morbidity and, therefore, a link between it and long-term survival cannot be established. The use of CR-POSSUM has been recommended as the most suitable for surgical practice²².

Pelvic exenteration postsurgical morbidity widely varies, from 37% to 100%, as reported by Yang et al.²³. Our results show major complications in 27.7% of patients, including infections, postsurgical bleeding, thromboembolic events, and death. These results compare favorably with those reported by Nielsen et al.²⁴ and by the Royal Marsden group (34.5-42.2%)²⁵. As we found in our series, surgical wound infection and pelvic abscess/collection are referred as the most common complications in other series²⁶. Our analysis shows that patients with an ASA score ≥ 3 had higher morbidity ($p = 0.036$). Even after standardization based on the type of procedure, a strong association has been found between ASA physical status and postsurgical morbidity for colorectal surgery²⁶.

Intraoperative bleeding $\geq 1,000$ mL was a statistically significant variable for postoperative mortality ($p = 0.043$), as well as for major morbidity ($p = 0.047$). This could probably be related to the type of procedure and the number of resected compartments, since six of the seven cases that met this parameter had more than three pelvic compartments resected according to the Royal Marsden Hospital classification²⁶. Hsu et al.²⁷ point out that pelvic exenteration encompasses a group of complex surgeries that include the resection of multiple organs. Removal of these tissues at the endopelvic fascia creates a large dead space that predisposes to abscess formation and would explain the high rate of complications.

Table 4. Univariate analysis of factors associated with 5-year overall survival and disease-free survival

	n (%)	5-year OS		5-year DFS	
		%	p	%	p
Age			0.905		0.179
< 60 years	9 (50)	44.4		33.3	
> 60 years	9 (50)	44.4		44.4	
Gender			0.031		0.891
Males	4 (22.2)	25		0	
Females	14 (77.7)	25		50	
Neoadjuvant therapy			0.557		0.282
Yes	12 (66.7)	33.3		25	
No	6 (33.3)	66.6		66.6	
Margin status			0.992		0.712
R0	16 (88.9)	43.7		37.5	
R1	2 (11.1)	50		50	
LVI			0.830		0.017
Yes	5 (27.8)	0		0	
No	13 (72.2)	61.5		53.8	
PNI			0.484		0.064
Yes	4 (22.2)	50		25	
No	14 (77.8)			42.8	
Lymph nodes			0.641		0.402
N0	13 (72.2)	38.4		30.7	
N+	5 (27.8)	60		60	
Metastatic disease			0.454		0.67
M0	15 (83.3)	53.3		46.6	
M+	3 (16.7)	0		0	
Adjuvant therapy			0.884		0.202
Yes	10 (55.6)	30		20	
No	8 (44.5)	62.5		62.5	
CR-POSSUM			0.095		0.376
> 10	8 (44.5)	37.5		37.5	
< 10	10 (55.5)	50		40	
Date of surgery			0.461		0.429
After 2010	10 (55.6)	70		20	
Up to 2010	8 (44.5)	50		62.5	

CR-POSSUM: Colorectal Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity; DFS: disease-free survival; LVI: lymphovascular invasion; OS: overall survival; PNI: perineural invasion.

Therefore, we believe that a more complex procedure is associated with higher mortality and more morbidity.

Despite lower morbidity rates being found in surgeries practiced after 2010, there were no significant differences in terms of major morbidity according to the year the procedures were carried out (60 vs. 40%; $p = 0.618$). Several factors have influenced the results in recent years, such as the integration of broad-spectrum antibiotics, thromboembolic prophylaxis, advanced energy surgical devices, surgical experience and critical care

teams²⁸. As a result, more prolonged long-term survival has been achieved with acceptable morbidity in selected patients at specialized units.

Complete resection (R0) was achieved in most patients, which compares favorably with other published series²⁹. Negative resection margins are known to be associated with significantly longer survival, but the proportion of patients with R1-R2 resection is substantially higher in other series^{30,31} and, therefore, this association cannot be established in our series.

Several authors report the results of pelvic exenteration for colorectal cancer with wide variation in terms of survival, which reflects the limited sample sizes at some study centers. In our series, 5-year survival compares similarly with that referred in the literature, which is 46-66%³²⁻³⁴. OS and DFS were 44.4% and 38.8%, respectively. Katory et al.³⁵ have published a series of 14 patients undergoing pelvic exenteration for colorectal cancer, with a 5-year OS higher than 80% being achieved. These findings are consistent with those of our series, with a higher OS being found in patients operated after 2010, although the relationship between the year of the procedure and survival was not shown to be significant (70 vs. 50%; $p = 0.461$).

Retrospective studies have identified prognostic factors associated with better outcomes that are consistent with those already recognized for rectal cancer, including stage, lymph node involvement and positive surgical margins^{34,36}. Our series did not identify these variables as being statistically significant.

The univariate analysis showed that the female gender is a highly significant factor for survival ($p = 0.03$). To our knowledge, no series has established the female gender as a factor of poor prognosis for survival. Lymphovascular invasion was the most important prognostic factor that was identified, with statistical significance for DFS ($p = 0.017$). Perineural invasion also showed a trend towards statistical significance ($p = 0.064$). Lymphovascular invasion has been shown to be an independent prognostic factor for recurrence and mortality in colorectal surgery^{36,37}. Both variables are believed to denote an aggressive phenotype, poor differentiation and higher invasive capacity, and therefore have an impact on DFS in patients with colorectal cancer³⁸.

Limitations

Our study has limitations, such as its retrospective nature, a small sample size, and heterogeneous

inclusion of patients with primary and recurrent rectal cancer. As previously mentioned, there have been changes in clinical practice during the study period, such as staging, neoadjuvant therapy, surgical techniques, etc., and, therefore, this series may not reflect contemporary surgical practice for pelvic exenteration. In the absence of randomized trials for any of these outcomes, clinicians must rely on data from non-controlled or cohort studies for this group of patients. It is important to continue to register patients who undergo pelvic exenteration in order to determine whether the statistical significance of those factors identified in this study remains constant.

Conclusions

In conclusion, pelvic exenteration is an aggressive procedure with considerable morbidity and mortality, which are acceptable due to the type of extended and radical surgery it represents. It is a well-known fact that these benefits decrease in cases where R0 resection cannot be achieved, which increases the risk of postsurgical complications. We believe it is important to use predictive scores, such as CR-POSSUM, in order to properly select patients who may be candidates for pelvic exenteration. In our series, the presence of lymphovascular invasion on final pathology was identified to be a factor of poor prognosis for DFS.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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