Outcome in patients with resectable locally recurrent rectal cancer after total mesorectal excision with and without previous neoadjuvant radiotherapy for the primary rectal tumor

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Abstract

Background

The widespread use of neoadjuvant radiotherapy (nRTx) followed by total mesorectal excision (TME) introduced the problem of treating locally recurrent rectal cancer (LRRC) after nRTx and TME. Few data exist on the outcome of the surgical treatment of this type of LRRC and the influence of nRTx for the primary tumor on the outcome is unclear.

Methods

All patients receiving multimodality treatment (including intraoperative radiotherapy) for LRRC in our center between 1996 and 2012 were retrospectively analyzed. The outcome of patients with non-metastasized resectable LRRC who received nRTx and TME for the primary tumor was compared to the outcome of patients who did not receive nRTx for the primary tumor.

Results

During this period, 139 patients underwent surgery for LRRC; 93 of these patients underwent curative surgery for LRRC after TME for the primary tumor. Sixty-five patients did not receive nRTx for the primary tumor, while 28 patients received nRTx for the primary tumor. There were no significant differences in the number of incomplete resections or peri-operative morbidities. There was no significant difference in 5-year overall survival (28% vs. 43%,p=0.81), recurrence-free survival (55% vs. 48%,p=0.50) and disease-free survival (27% vs. 40%,p=0.59).

Conclusion

Surgical treatment of carefully selected patients with non-metastasized resectable LRRC after nRTx and TME for the primary tumor is feasible and can result in sustained local control and overall survival. Patients with resectable LRRC who received nRTx for the primary tumor do not have a poorer outcome than patients who did not.

Introduction

Before the introduction of total mesorectal excision (TME) for rectal cancer, local recurrence rates after surgery varied between 15 and 45%.[1-3] Since the publication of the Dutch TME-trial, neoadjuvant radiotherapy (nRTx) followed by TME became the standard of care in the Netherlands for stage II and III rectal cancer and has led to a decrease in local recurrence rates to 6%.[4] The implementation of nRTx and TME as standard therapy introduced the problem of treating locally recurrent rectal cancer (LRRC) after nRTx and TME.

Surgical treatment of LRRC includes (chemo-)radiotherapy to improve local control.[5] When nRTX was administered for the primary tumor, the radiation dose for treatment of the LRRC is limited.[6] In addition, recurrences after TME may not be limited to the anatomical compartment lined by the visceral rectal fascia. Both factors render radical resection of these recurrences more demanding than resection in patients who did not undergo nRTx or TME previously. However, literature on the outcome of surgical treatment of LRRC after TME with and without nRTx for the primary tumor is scarce.

According to an update of the Dutch TME-trial, patients with LRRC after nRTx for the primary tumor have a shorter overall survival than patients who did not receive nRTx for the primary tumor.[7] This suggests that local recurrences after nRTx for the primary tumor have a more aggressive biological behavior than recurrences of rectal cancer that was not treated with nRTx primarily.

Because of the factors mentioned above, it is questionable whether curative treatment of LRRC in these patients is possible. On the other hand, if curative resection is possible the influence of nRTx for the primary tumor on outcome is unclear. The aim of the current study was to evaluate the outcome of resectable LRRC after nRTx and TME for the primary tumor and to demonstrate whether there is a difference in outcome of the curative treatment of resectable LRRC in patients who received nRTx and TME for the primary tumor and patients who had TME without nRTx.

Patients and Methods

Between January 1996 and July 2012, all patients undergoing surgery for LRRC in our hospital, a tertiary referral center for the southwest region of the Netherlands, were entered in a prospective database and retrospectively analyzed. All patients had a histologically proven recurrence of rectal cancer in the pelvic area.

Patients were divided into two groups; group A were patients who did not receive nRTx for the primary tumor, group B were patients who received nRTx for the primary tumor. Only primary resections that were performed by TME were included.

All LRRCs were scheduled for neoadjuvant (chemo-)radiotherapy followed by surgery. Patients who received nRTx for the primary tumor received a neoadjuvant re-irradiation dose of 27-30Gy, delivered in 15-18 fractions of 1,8-2Gy. Patients who did not receive nRTx for the primary tumor were scheduled for 44.6-52Gy in 19-28 fractions of 1.8-2.3Gy. (Re-)irradiation for LRRC was administered by a 3- or 4 field-technique or by 5 fields using intensity modulated radiotherapy. From 2006 onwards, all patients received chemoradiotherapy with capecitabine administered orally at a dose of 825 mg/m^2 twice a day during radiotherapy days as reported previously.[8] Before 2006, no patient received concomitant chemotherapy.

Before treatment, distant metastases were ruled out by a thoraco-abdominal CT-scan, which was repeated after (re-)irradiation.[9] In the majority of patients, pelvic MRI was performed for localization and progression of the recurrence prior to and after (re-) irradiation. Resectable LRRC was defined as a recurrence within the pelvic region, without distant metastases in which imaging revealed a recurrence with a high chance of a R0/R1-resection. R0/R1-resection was considered feasible when there was no apparent lateral bone-involvement, no sacral involvement above level S3, no extension through the greater sciatic notch and no encasement of common or external iliac arteries. Local recurrences were classified using the Wanebo classification.[10]

All surgical procedures were performed by a midline abdominal approach and included low anterior resections (LAR), abdominoperineal resections (APR), posterior or total exenterations and abdominoperineal-sacral resections. R0-resections were defined as resection margins >0mm; R1-resections as microscopically involved resection margins and R2-resections as macroscopically involved resection margins. Our multimodality approach for LRRC includes intra-operative radiotherapy (IORT) with a single dose of 10Gy for patients with tumor-free margins ≤2mm, evaluated during surgery on frozen sections.[11] No patient received adjuvant chemotherapy.

Peri-operative morbidity was divided into surgical and non-surgical morbidity. Abdominal wound infections were scored in case there were signs of inflammation. Wound healing problems after APR were defined as signs of inflammation of the perineal area 30 days after surgery. A presacral abscess was diagnosed by clinical symptoms in combination with a CT-scan. Small bowel obstruction and postoperative hemorrhage were considered adverse events when a re-laparotomy had to be performed. Post-operative complications were graded according to the Dindo-Clavien classification.[12] Peri-operative mortality was defined as any death occurring within 30 days of surgery. In-hospital mortality was defined as any death occurring during admission.

Statistical analysis was carried out using SPSS (version 20.0.0.1). Data was reported as median (interquartile range). The Chi-square (χ^2), Fisher's exact and Mann-Whitney U test were used for comparison of both groups as appropriate. The survival rates were calculated using Kaplan-Meier curves and significance was calculated by a log rank test.

Survival rates were calculated from the day of LRRC surgery until death or last follow-up. P-values ≤0.05 were considered significant.

Results

A total of 139 patients underwent surgery for LRRC between January 1996 and July 2012. In 98 patients primary tumor resection was performed by TME. During LRRC surgery, 5 of 98 patients were considered incurable due to metastatic disease or unresectability of the recurrence, rendering 93 patients eligible for analysis. Of these patients, 65 did not receive nRTx for the primary tumor (group A), while 28 patients received nRTx for the primary tumor (group B).

Table I. Patient and primary tumor characteristics

	No nRTx for primary tumor (group A)	nRTx for primary tumor (group B)	P-value
Total patients	65	28	
Age (years) ‡	66 (59-72)	63,5 (55-70)	0.23*
Gender			
Male	46 (65)	18 (64)	-
Female	19 (35)	10 (36)	0.54**
Primary tumor stage			
Stage I	12 (18)	5 (18)	-
Stage II	26 (40)	8 (29)	-
Stage III	22 (34)	11 (39)	-
Stage IV	3 (5)	4 (14)	-
Unknown	2 (3)	0	0.39**
Type resection			
LAR	45 (69)	17 (61)	-
APR	20 (31)	11 (39)	0.42**
Neoadjuvant treatment			
Short course RTx (25Gy)	-	10 (36)	-
Long course RTx (44.6 -50Gy)	-	10 (36)	-
Chemoradiotherapy (50Gy)	-	8 (28)	-

*Values in parentheses are percentage unless indicated otherwise; nRTx, neoadjuvant radiotherapy;‡, values are median (interquartile range); LAR, Low Anterior Resection; APR, Abdominoperineal Resection; RTx, Radiotherapy; *, using Mann Whitney U test; ** using χ^2-test*

Primary tumor and local recurrence

Patient and primary tumor characteristics are depicted in *table I*. All patients with stage IV primary rectal cancer (n=7) had undergone metastasectomy previously (median 14

months prior to LRRC, range 12-48 months) and were free of distant metastases at the time of diagnosis of LRRC. The median interval between primary tumor resection and diagnosis of LRRC was 24 (14-41) months for the patients in group A and 20 (12-30) months for patients in group B (p=0.10). The tumor characteristics of LRRC are depicted in *table II*

Table II. Tumor characteristics of locally recurrent rectal cancer

	No nRTx for primary tumor (group A)	nRTx for primary tumor group B)	P-value
Total patients	65	28	
Wanebo classification			
Tr1	7 (11)	1 (4)	-
Tr2	6 (9)	3 (11)	-
Tr3	24 (37)	12 (39)	-
Tr4	23 (36)	11 (36)	-
Tr5	5 (8)	1 (4)	0.74**
Location of recurrence			
Intraluminal	13 (20)	4 (14)	-
Extraluminal	52 (80)	24 (86)	0.51***
Location of LRRC			
Presacral	21 (32)	10 (36)	-
Lateral	18 (28)	8 (29)	-
Anterior	15 (23)	6 (21)	-
Anastomic	13 (20)	4 (14)	0.92**

*Values in parentheses are percentage; nRTx, neoadjuvant radiotherapy; Tr, Tumor stage recurrent rectal cancer; LRRC, locally recurrent rectal cancer; ** using χ^2-test, *** using Fisher's exact test*

Peri-operative results

The surgical procedures and operative results for LRRC are depicted in *table III*. There were no significant differences between both groups in the number of R0, R1 and R2-resections, although there tend to be more R1-resections in group B (26% vs. 43%,p=0.09). Intraoperative radiotherapy (IORT) was administered to all patients with an R1-resection or with a tumor-free margin ≤2mm.

Table III. Operation characteristics for locally recurrent rectal cancer

	No nRTx for primary tumor (group A)	nRTx for primary tumor (group B)	P-value
Total patients	65	28	
Neoadjuvant treatment LRRC			
RTx	41 (63)	11 (39)	
CTxRTx	24 (37)	17 (61)	0.03**
Interval nRTx and surgery‡	8 (6 – 10)	8 (8 – 10)	0.46*
Surgical procedure			
LAR	7 (11)	1 (4)	-
APR	15 (23)	7 (25)	-
Intersphinteric resection	4 (14)	1 (4)	-
Posterior exenteration ¥	17 (26)	10 (36)	-
Total pelvic exenteration	17 (26)	8 (29)	-
Pelvic recurrence resection	5 (8)	1 (4)	0.76**
Partial sacrectomy	5 (8)	2 (7)	0.93***
Omental flap	43 (66)	18 (64)	0.86**
Resection margin			
R0	41 (63)	13 (46)	-
R1	17 (26)	12 (43)	-
R2	7 (11)	3 (11)	0.26**
IORT			
R0†	16/41 (39)	6/13 (46)	0.65**
R1	17/17 (100)	12/12 (100)	-
R2	5/7 (71)	3/3 (100)	1.00***
Pathological complete response	6 (9)	1 (4)	0.67***
Operation time (minutes) ‡	408 (268 – 491)	460 (360 – 555)	0.14*
Blood loss (milliliters) ‡	2200 (1925 – 3900)	3900 (1925 – 8250)	0.16*

*Values in parentheses are percentage; †, values in parentheses are interquartile range; RTx, Radiotherapy; CTxRTx, chemoradiotherapy; LAR, Low Anterior Resection; APR, Abdominoperineal Resection;¥, only performed in women, percentage of all patients; R0, resection margin of >0 mm; R1, microscopically invclved margins; R2, macroscopically involved margins; IORT, intraoperative radiotherapy; † only in patients with margins <2mm *, using Mann-Whitney U test; **, using χ^2-test; ***, using Fisher's exact test*

In group A, 41 surgical complications occurred in 32 patients (49%). Sixteen surgical complications occurred in 13 patients (46%) in group B (p=0.80). Seventeen non-surgical complications occurred in 12 (18%) patients in group A and 11 non-surgical complications occurred in 8 patients (29%) in group B (p=0.28). There was no significant difference in grade ≥2, ≥3 or ≥4 complications.

Three patients (3%) died during admission in the hospital. There was no significant difference in in-hospital or peri-operative mortality between both groups. All deaths were caused by cardiac events. The peri-operative morbidity and mortality is further outlined in *table IV*.

Table IV. Mortality and peri-operative morbidity

	No nRTx for primary tumor (group A)	nRTx for primary tumor (group B)	P-value
Total patients	65	28	
Peri-operative morbidity			
Surgical			
Abdominal wound infections	11 (17)	5 (18)	1.00***
Presacral abscess	11 (17)	5 (18)	0.91**
Relaparotomy	10 (15)	3 (11)	0.75***
Small bowel perforation	5 (8)	1 (4)	-
Wound dehiscence	1 (4)	0	-
Abscess/hemorrhage	2 (2)	1 (4)	-
Negative	2 (4)	1 (4)	-
Non-surgical			
Pneumonia/atelectasis	9 (14)	4 (14)	0.73***
Cardiac	3 (5)	2 (8)	0.64***
Urinary tract infection	5 (8)	5 (18)	0.19**
Perineal woundhealing problems^	12 (70)	8 (66)	1.00**
Grading of complications (Dindo-Clavien)			
Grade ≥2	45 (78)	22 (81)	0.68**
Grade ≥3	24 (41)	10 (37)	0.70**
Grade ≥4	9 (16)	3 (11)	0.74***
Mortality			
In hospital mortality	1 (2)	2 (7)	0.22***
Peri-operative mortality	3 (5)	2 (7)	0.64***

*Values in parentheses are percentage; nRTx, neoadjuvant radiotherapy; ^, only in patients with an APR **, using χ^2-test; ***, using Fisher's exact test*

Survival

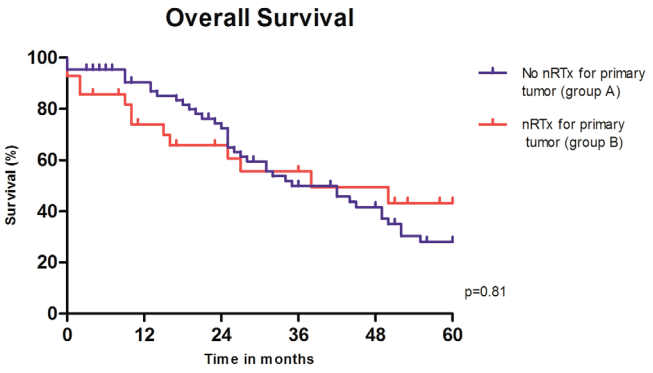
In group A, 25 patients (39%) were alive at last follow up. The median survival of surviving patients was 41 (range, 3-90) months. In group B, 14 patients (50%) were alive at last follow up. Their median survival was 32 (range, 4-86) months. The median survival of all patients in group A was 42 (95%CI 27-57) months compared to 38 (95%CI, 0-77) months for all patients in group B (p=0.81). The estimated 3- and 5-year overall survival rates of patients in group A were 50% and 28% respectively and for patients in group B 56% and 43%, respectively. *(Fig. IA)*

In group A, 23 (35%) patients suffered a re-recurrence, while 21 patients (32%) died without suffering a re-recurrence. This resulted in an estimated 5-year local recurrence-free survival of 55%. In group B, 11 patients (39%) suffered a local re-recurrence, while

5 patients (18%) died without suffering a re-recurrence. This resulted in an estimated 5-year local recurrence-free survival of 48%. This did not differ significantly from group A. (p=0.50) *(Fig. IB)*

There was a significant difference in distant metastasis free-survival after 5 years in favor of patients in group B (39% vs. 66%,p=0.05). These results are shown in *figure IC*. Disease free-survival did not differ significantly after 5 years (27% vs. 40%,p=0.59) and is shown in *figure ID.*

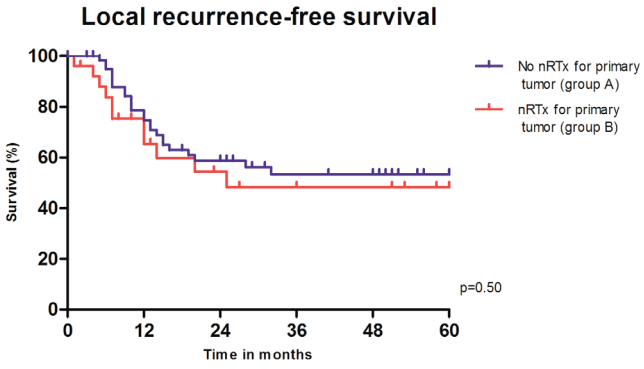
Figure Ia: Overall survival



Patients at risk

No nRTx (group A)	65	52	39	26	20	10
nRTx (group B)	28	18	13	10	8	3

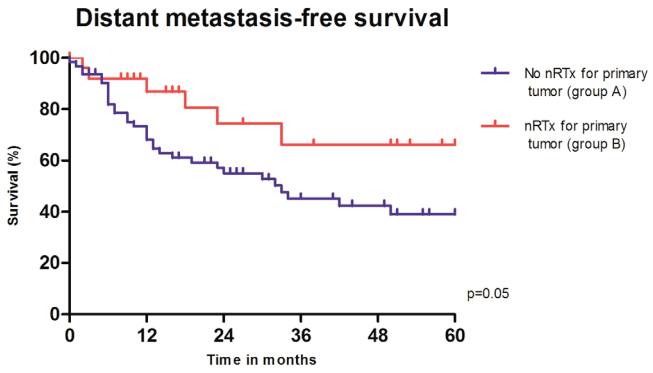
Figure IB: Local recurrence-free survival



Patients at risk

No nRTx (group A)	65	41	27	19	18	9
nRTx (group B)	28	15	9	7	7	2

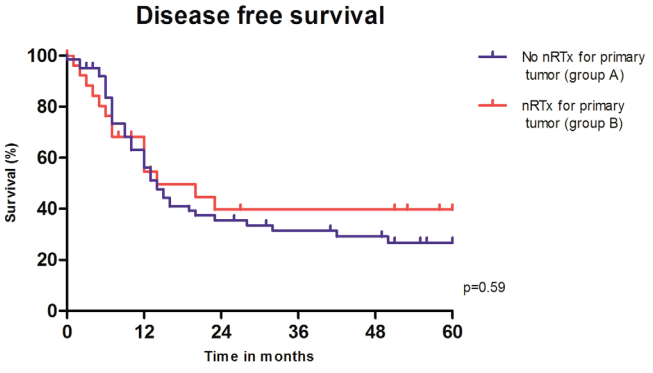
Figure IC: Distant metastasis-free survival



Patients at risk

No nRTx (group A)	65	41	27	18	14	9
nRTx (group B)	28	18	13	8	8	2

Figure ID: Disease free survival



Patients at risk

No nRTx (group A)	65	37	19	15	13	8
nRTx (group B)	28	15	9	7	7	2

Discussion

Our results demonstrate that in carefully selected patients with non-metastasized resectable LRRC who received nRTx and TME for the primary tumor, the overall survival is similar to patients who did not receive nRTx for the primary tumor. There may be more incomplete resections in patients who received nRTx for the primary tumor, but this does

not result in an increased local re-recurrence rate. The peri-operative morbidity is not increased in patients who received nRTx for the primary tumor.

These findings are complementary to updates of two large randomized controlled trials[7,13] These studies demonstrated a poorer prognosis of LRRC in case the primary tumor was treated with nRTx. However, both studies included patients that were treated curatively and those who were not, while our study focuses on resectable LRRC specifically. The poorer prognosis of LRRC after nRTx may lead to the conclusion that nRTx alters tumor characteristics resulting in more aggressive biological behavior. However, it is more likely that recurrences after nRTx may simply represent a selection of patients with unfavorable tumor characteristics. Neoadjuvant radiotherapy probably does not prevent recurrence in patients with "bad" disease (e.g. more residual disease, positive resection margins, higher tumor load). These patients are likely to have a poorer prognosis and this originates in *a high rate of distant* metastases at diagnosis or within 6 months after diagnosis of LRRC after nRTx for the primary tumor.[7] These distant metastases disqualify patients for surgery and this caused only a minority (17%) of the patients after nRTx in the update of the Dutch TME-trial to be selected for curative surgery. In our hospital, since 2002, 28% of patients with LRRC after nRTx for the primary tumor were scheduled for curative treatment (data not shown). By ruling out distant metastases prior to and after (re-)irradiation, we only selected those patients that in general have malignancies with a more benign biological behavior and this explains why this study did not find a difference in outcome of patients treated with and without nRTx for the primary tumor.

Surprisingly, we found a significant difference in 5-year distant metastasis-free survival in favor of patients who received nRTx for the primary tumor. This finding should be interpreted with caution. It is based on a small number of patients and is probably caused by the selection bias mentioned above. However, it may explain why the outcome in these patients is comparable to that of patients who did not receive nRTx for the primary tumor, even when re-irradiation doses are limited and radical resections are technically more demanding. The difference in distant metastasis-free survival did not result in a significant difference in overall survival, which is comparable to the overall survival in other centers where a multimodality approach for LRRC is adapted.[14,15]

Because resected LRRC patients in both study groups have a similar local recurrence-free survival, this implies that previous irradiation for the primary tumor does not result in decreased local control after surgery for the LRRC. This is remarkable, because the number of R0-resections in patients who received nRTx for the primary tumor was lower (although not significant) and radical resection is the most important prognostic factor for local re-recurrence and overall survival after resection of LRRC.[16-18] This lower number of R0-resections could be explained by the fact that a re-irradiation dose of 30Gy is less effective than an irradiation dose 50Gy, resulting in less downstaging and

more incomplete resections. LRRC in patients who received nRTx for the primary tumor may also evolve from radiation-insensitive tumor deposits, rendering re-irradiation less effective. Nonetheless, our R0-resection rate of LRRC in patients who did and did not receive nRTx for the primary tumor is in line with other studies that report radical resection rates of 44-59% in LRRC after TME for the primary tumor. These studies did not include patients that had received nRTx or did not differentiate between patients who did and did not receive nRTx for the primary tumor.[19,20]

IORT may be a contributing factor to the relatively low local recurrence rate after R1-resections in this study. Although no randomized control trials were published proving the value of IORT for LRRC, several retrospective studies suggested a beneficial effect of IORT on local control for locally advanced rectal cancer.[21-23] In IORT, the biological equivalent of a single dose is considered 2 to 3 times the dose given by conventional fractioning.[24] The biological equivalent dose (BED) of 30Gy re-irradiation is 36Gy, resulting in a combined BED of nRTx and IORT of 56-66Gy, which is an adequate dose to increase local control in rectal cancer. In patients who received an irradiation dose of 50Gy, which has a BED of 60Gy, the addition of IORT leads to a BED of 80-90Gy. However, this did not result in a lower local recurrence rate in our study.

Although there was more blood loss in patients with LRRC who received nRTx for the primary tumor, peri-operative morbidity and mortality rates were similar in both groups. Increased blood loss may be caused by extensive post-radiation fibrosis after previous nRTx and re-irradiation. Overall complication rates, the occurrence of wound infections and presacral abscesses were similar to those reported in the literature.[14,18,19,25]

As could be expected in a retrospective analysis, this study has methodological drawbacks. Patients eligible for surgery were selected from larger groups of patients that were not selected for surgery because of distant metastases, unresectable disease or co-morbidity. In the first years of our study period, patients often did not receive nRTx for the primary tumor, whereas in later years, neoadjuvant therapy became the standard. This resulted in a difference in length of follow-up of 9 months of the surviving patients between groups A and B (41 vs. 32 months). Despite this difference, we think both groups were followed for an adequate length of time, since no re-recurrences were reported after 32 months of follow up. Furthermore, during the study period imaging modalities have improved, possibly resulting in more accurate staging and improved patient selection.

In conclusion, surgical treatment of carefully selected patients with resectable LRRC without metastatic disease after nRTx and TME is feasible and can result in sustained local control and overall survival. Patients with resectable LRRC after nRTx and TME for the primary tumor do not have a poorer outcome than patients who did not receive nRTx for the primary tumor. Therefore, these patients should be considered candidates for curative surgery. However, only a minority of patients with LRRC after previous irradiation

are candidates for curative surgery, because the majority has distant metastases or unresectable disease. Patients after previous nRTx for the primary tumor are more likely to have an incomplete resection of the LRRC, but this does not result in an increased local recurrence rate in this series of patients who underwent multimodality treatment.

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