

Original Article



Surgical Outcomes Associated with Operable Gastric Cancer in a Tertiary Care Indian Hospital

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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ABSTRACT

Purpose: Data on operable gastric cancer from India is sparse. The purpose of this study was to investigate the clinical details, histopathological demographics, and 5-year overall survival (OS) and disease free survival (DFS) associated with operable, non-metastatic gastric cancer in a dedicated upper gastrointestinal (GI) surgical unit in India.

Materials and Methods: Data for patients diagnosed with operable gastric cancer between January 2006 and December 2014 were retrospectively analyzed. Data were collected from electronic hospital records in addition to mail and telephonic interviews when possible.

Results: A total of 427 patients were included. The tumor was located in the pyloro-antral region in 263 patients (61.7%). Subtotal gastrectomy was performed in 291 patients and total gastrectomy in 136 patients. Tumor stage classification revealed 43 patients (10.0%) with stage I, 40 patients (9.4%) with stage IIA, 59 patients (13.9%) with stage IIB, 76 patients (17.8%) with stage IIIA, 96 patients (22.5%) with stage IIIB, and 113 patients (26.4%) with stage IIIC disease. Follow-up data were available for 71.6% of the patients with a mean duration of 32.4 months. Five-year DFS and OS were 39% and 59%, respectively.

Conclusions: Despite presenting at an advanced stage, the 5-year DFS and OS of patients with operable gastric cancer treated at a dedicated upper GI unit of a tertiary care center in India was good.

Keywords: Carcinoma; Stomach; Epidemiology; India; Gastrectomy; Survival

INTRODUCTION

The overall 5-year survival associated with gastric cancer in India has been estimated to be between 4% and 15% [1,2]. This is less than that reported from most Western countries and other Asian countries [3]. Available data on operable, potentially curable gastric cancers in India is sparse. This has been highlighted by Sharma et al. [4] who also report the need for robust cancer survival data. The disease presentation and results of operable gastric cancer therapy differ among American, European, and Asian countries. Therefore, extrapolating international findings without any available Indian data would be speculative. We present our experience of treating operable, non-metastatic gastric cancer over a 9-year period. To our knowledge, this is the largest reported series from India.

MATERIALS AND METHODS

The study was conducted in a dedicated upper gastrointestinal (GI) unit of a tertiary care teaching hospital in South India after obtaining the Institutional Review Board (IRB) clearance (Approval No. 10204). The study was performed in accordance with ethical principles for medical research as outlined in the Declaration of Helsinki. Data for patients who underwent subtotal or total gastrectomy for operable, non-metastatic gastric cancer between January 2006 and December 2014 were retrospectively studied. Electronic hospital records were used to collect data on clinical parameters, histopathological staging, and the type of surgery. Follow-up and survival data were collected from telephonic interviews, electronic mails, and electronic hospital records. Patients with gastro-esophageal junction tumors and palliative gastric resections were excluded from the study.

As per the protocol, all patients underwent pre-operative cross-sectional imaging (i.e. computed tomography [CT] of the abdomen) and upper GI endoscopy for tumor visualization and biopsy for histological confirmation. Operability was assessed based on the pre-operative contrast enhanced CT results and cases of all patients were discussed during the upper GI multi-disciplinary tumor board meeting. A diagnostic laparoscopy was performed prior to performing definitive surgery from the year 2010.

The surgical procedures performed included a radical total or subtotal gastrectomy depending on the location of the primary tumor. If the tumor infiltrated an adjacent organ, a multi-visceral resection was performed, provided that an R0 resection was possible. A D1+ or a D2 lymphadenectomy was performed in the majority of our patients [5].

Histopathological staging was done using the tumor, node, metastasis (TNM) classification as defined by the American Joint Committee on Cancer (AJCC), 7th edition [6]. Following the surgical treatment, cases of all patients were re-discussed during the upper GI multidisciplinary tumor board meeting and the plan for adjuvant therapy was finalized. Patients who were at a disease stage >T2, N0 were administered adjuvant therapy. The adjuvant therapy included 5-fluorouracil and cisplatin in the initial study period (2004–2010). However, since 2011, oxaliplatin, docetaxel, and oral capecitabine are used. Administration of perioperative (neoadjuvant) chemotherapy was commenced in 2014; therefore, only eight patients in the study group fell into this category. In this series, the majority of patients underwent upfront surgery followed by adjuvant chemotherapy/chemo radiotherapy. The type of therapy was tailored according to the stage of the disease, general condition of the patient, and the logistic difficulties faced by patients in view of the long travelling distances to avail treatment.

The patients were followed up in the surgical outpatient and the medical/radiation oncology outpatient clinics on a regular basis. Anastomotic leak was diagnosed as any clinical or radiological leak of GI contents.

Data were analyzed using SPSS for Windows (version 16.0; SPSS Inc., Chicago, IL, USA). Statistical significance for individual variables was analyzed using the χ^2 and Fisher's exact test for categorical variables and t-test for continuous variables. Survival analysis was performed using Kaplan-Meier curves and compared using log rank (Mantel-Cox) test. The number at risk analysis was assessed using StataCorp, 2013 (Stata Statistical Software: Release 13; StataCorp LP software, College Station, TX, USA).

RESULTS

Four hundred and twenty-seven patients underwent gastric resections for operable, non-metastatic gastric cancer. Subtotal gastrectomy with Roux-en-Y gastrojejunostomy was performed in 291 patients and total gastrectomy with Roux-en-Y oesophagojejunostomy was performed in 136 patients.

The mean age of patients with gastric cancer was 52 years (range 23–84 years). The baseline demographics of patients in the study cohort are presented in **Table 1**.

Surgical details such as the extent of lymphadenectomy, R0/R1/R2 resection, multi-organ resection, the length of hospital stays, the details of postoperative complications, early post-

Table 1. Baseline demographics of patients with operable non-metastatic gastric cancer

Variables	No. (%)
Age (yr)	
≤50	169 (39.6)
>50	258 (60.4)
Sex	
Male	301 (70.4)
Female	126 (29.6)
BMI (kg/m²)	
<18.5	114 (26.7)
18.5–25.0	244 (57.1)
26.0–30.0	45 (10.5)
>30.0	24 (5.6)
Comorbid illnesses	
Diabetes mellitus	70 (16.4)
Hypertension	66 (15.4)
Ischemic heart disease	25 (5.9)
Chronic kidney/pulmonary disease	24 (5.6)
ASA score	
1	105 (24.6)
2	227 (53.2)
3	90 (21.0)
4	5 (1.2)
Location of tumor	
Antropyloric region	263 (61.6)
Body	117 (27.4)
Fundus	38 (8.9)
Cardia	6 (1.4)
Diffuse	3 (0.7)
Neoadjuvant therapy	8/427 (1.8)
Adjuvant therapy	
Yes	336 (78.6)
No	68 (16.0)
Missing data	23 (5.4)
No. of operations in each year	
2006	40
2007	41
2008	43
2009	41
2010	41
2011	48
2012	56
2013	58
2014	59

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

operative mortality (within 30 days) are summarized in **Table 2**. Gastrectomy was performed using the open technique in all patients.

A total of 40 patients had local infiltration to the adjacent organs such as the colon (n=9), pancreas (n=19), liver (n=3), and spleen (n=8). Extended multi-visceral resection (when feasible) was performed in 22 patients in our series. En-block colectomy was performed in nine patients, splenectomy in eight, distal pancreatectomy, and splenectomy in 2, while 2 patients underwent segment-3 liver en-block excision. In the cases where extended multi-visceral resection was not feasible, the tumor was grossly dissected off the adjacent organ.

The histopathological characteristics of operable gastric cancers are described in **Table 3**. The most common TNM stage of presentation was stage IIIC.

Follow-up data were available for 306 patients with a mean follow-up of 34.1 months (median=27 months). The 5-year disease free survival (DFS) and overall survival (OS) were 39.8% and 59.3% across all stages. The 3-year DFS and OS was 50.0% and 67.9%, respectively (**Fig. 1A and B**).

The stage wise 5-year DFS and OS are shown in **Fig. 2A and B**. Detailed stage wise 5-year DFS and OS breakup is shown in **Table 4**.

For the univariate analysis, stage of tumor, grade of the tumor, lymphovascular and perineural invasion, metastatic lymph node ratio (MLR; ratio of the positive nodes to total nodes sampled) [7-9], type of resection (R0/R1/R2), adequate lymphadenectomy (15 or more nodes harvested) [10], and grade of tumor were significant poor predictors of OS and DFS (**Tables 5 and 6**). However, for the multi-variable analysis, only stage of the tumor (P=0.049)

Table 2. Surgical characteristics

Variables	No. (%)
Type of surgery	
Sub-total gastrectomy	291 (68.1)
Total gastrectomy	136 (31.9)
Lymphadenectomy	
D0	36 (8.4)
D1+	259 (60.7)
D2	124 (29.1)
Missing	8 (1.8)
Resection	
R0	297 (69.6)
R1	70 (16.4)
R2	60 (14)
Multivisceral resection (n=22)	
Spleen	8
Distal pancreatico-splenectomy	2
Liver resection	3
Transverse colon	9
Post-operative complication (Anastomotic leak)	
Subtotal gastrectomy	20/29 (6.8)
Total gastrectomy	20/136 (14.7)
Average hospital stay (day)	
Subtotal gastrectomy	14
Total gastrectomy	17
30-day mortality	
Subtotal gastrectomy	11/291 (3.7)
Total gastrectomy	7/136 (5.1)

Table 3. Histopathological demographics

Histopathological parameters	No. (%)
Mucinous	19 (4.4)
Signet ring	67 (15.7)
Grade of tumor	
Well differentiated	12 (2.8)
Moderately differentiated	159 (37.2)
Poorly differentiated	246 (57.7)
Missing	10 (2.3)
T stage	
T1	31 (7.2)
T2	33 (7.8)
T3	166 (38.9)
T4a	157 (36.7)
T4b	40 (9.4)
N stage	
N0	88 (20.6)
N1	78 (18.2)
N2	100 (23.4)
N3	161 (37.8)
Staging	
Stage I	43 (10.0)
Stage IIA	40 (9.4)
Stage IIB	59 (13.9)
Stage IIIA	76 (17.8)
Stage IIIB	96 (22.5)
Stage IIIC	113 (26.4)
Mean nodes sampled	13 (SD±7.9)
Lymphovascular invasion	154 (36.1)
Perineural invasion	152 (35.6)
MLR*	
MLR0	87 (20.3)
MLR1	77 (18.1)
MLR2	94 (22.0)
MLR3	169 (39.6)

SD = standard deviation; MLR = metastatic lymph node ratio.

*MLR is ratio of total lymph nodes with tumor to total lymph nodes harvested—MLR0=0; MLR1>0–0.3; MLR2>0.3–0.6; MLR3>0.6.

and MLR ($P=0.047$) significantly predicted worse 5-year OS. Stage of the tumor ($P=0.048$) and MLR ($P=0.043$) significantly predicted the 5-year DFS on multivariable analysis.

The majority of patients included in the series were referred from the North-Eastern parts of India (44%); thus, the majority of participants had to travel more than 1,500 kilometers to reach the hospital. As a subset analysis, the demographics, histopathology, and survival were studied based on the patients' geographical distribution (**Table 7**). Patients from the North-Eastern part of India were 5 years younger than those from the Southern part ($P<0.01$). There was no difference in stage wise presentation, location of primary or the long-term survival statistics between patients of different geographical locations treated at our center.

DISCUSSION

Gastric cancer is the fifth and seventh most common cancer among Indian men and women, respectively, and the second most common cause of cancer related deaths [11,12]. Although multi-modal therapy can improve survival of gastric cancer patients, surgery is generally considered as the only treatment modality that can cure gastric cancer [13]. Most information

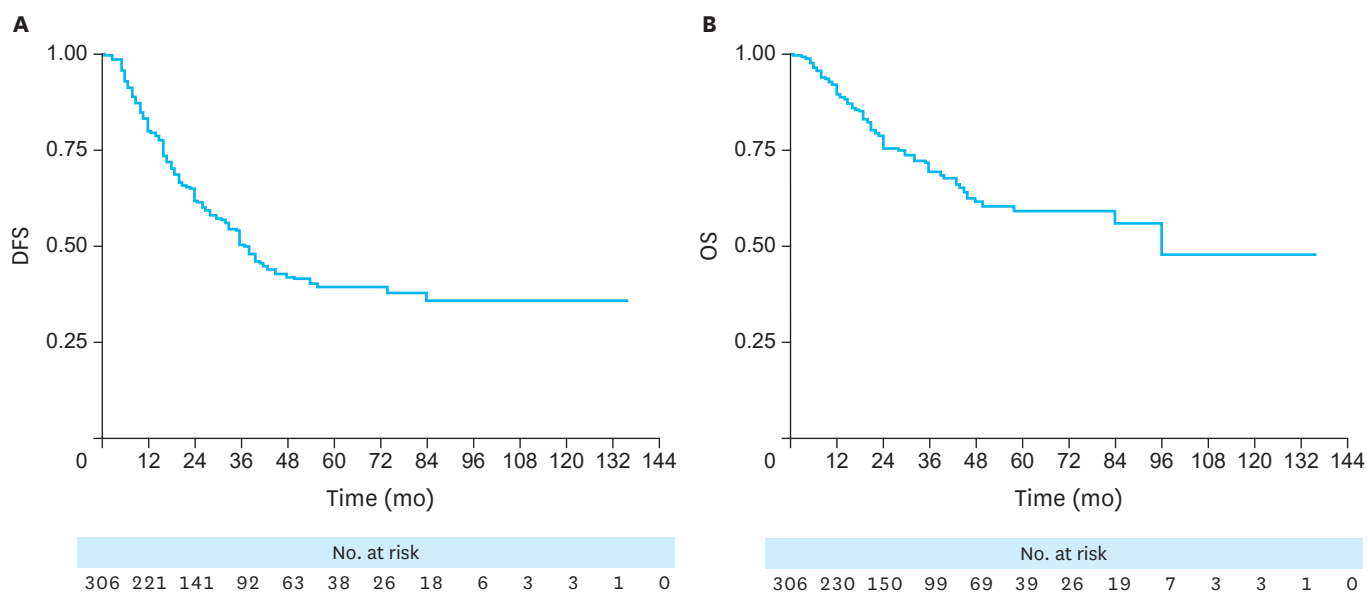


Fig. 1. Kaplan-Meier curve. (A) DFS; (B) OS. DFS = disease free survival; OS = overall survival.

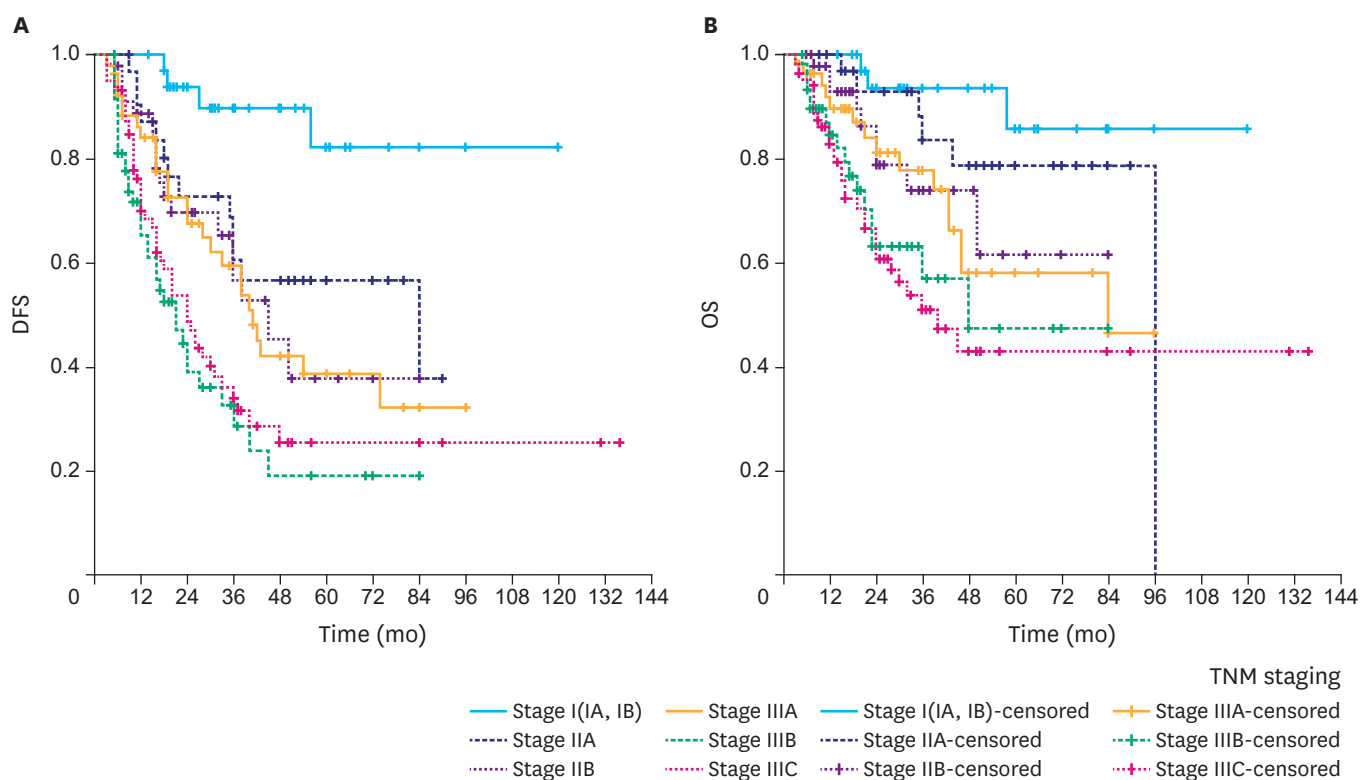


Fig. 2. Kaplan-Meier curve for stage wise. (A) DFS; (B) OS. DFS = disease free survival; OS = overall survival; TNM = tumor, node, metastasis.

pertaining to gastric cancer survival in India has been derived from epidemiology based cancer registries. Detailed analysis of prognostic factors and survival analysis of operable non-metastatic gastric cancer from India is however lacking.

Table 4. Stage wise 5-year OS and DFS

Staging	5-year OS	5-year DFS
Stage I	85.5	82.3
Stage IIA	78.5	46.5
Stage IIB	61.5	37.7
Stage IIIA	51.9	32.2
Stage IIIB	47.3	19.0
Stage IIIC	42.9	25.5

OS = overall survival; DFS = disease free survival.

The average age of presentation was 52 years, which is about fifteen years lower than reported from American cancer registries and a decade lower than reports from Asia [14,15]. Over 2/3 of patients in our series were male patient; the male preponderance is in line with data from the American cancer surveillance database, Surveillance, Epidemiology, and End Results (SEER) [16].

Table 5. Factors predicting poor OS on univariate analysis (n=306)

Variables	Total	Deaths	P-value*
Staging			<0.001
Stage I	35	3	
Stage IIA	32	6	
Stage IIB	46	9	
Stage IIIA	53	15	
Stage IIIB	59	17	
Stage IIIC	81	31	
Grade			0.071
Well	6	0	
Moderate	119	27	
Poor	181	51	
Lymphovascular invasion			0.021
Yes	104	34	
No	202	47	
Peri-neural invasion			0.001
Yes	116	41	
No	190	40	
Signet ring			0.991
Yes	43	13	
No	263	68	
Mucinous			0.131
Yes	14	5	
No	292	76	
Resection			0.011
R0	217	52	
R1	51	16	
R2	38	13	
DO vs. D1+ and D2			0.288
D1+/D2	279	71	
D0	23	10	
Nodes harvested			0.607
<15	183	45	
≥15	123	36	
MLR			<0.001
MLR0	73	12	
MLR1	52	12	
MLR2	67	18	
MLR3	114	39	

OS = overall survival; MLR = metastatic lymph node ratio.

*Log rank test.

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Table 6. Factors predicting recurrence on univariate analysis (n=306)

Variables	Total	Recurrence	P-value*
Staging			0.001
Stage I	35	4	
Stage IIA	32	13	
Stage IIB	46	17	
Stage IIIA	53	26	
Stage IIIB	59	35	
Stage IIIC	81	46	
Grade			0.026
Well	6	0	
Moderate	119	49	
Poor	181	87	
Lymphovascular invasion			0.026
Yes	104	54	
No	202	86	
Peri-neural invasion			0.022
Yes	116	60	
No	190	79	
Signet ring			0.776
Yes	43	23	
No	263	117	
Mucinous			0.181
Yes	14	7	
No	292	133	
Resection			0.012
R0	217	93	
R1	51	28	
R2	38	19	
D0 vs. D1+ and D2			0.395
D1+/D2	279	124	
D0	23	13	
Nodes harvested			0.042
<15	183	83	
≥15	123	58	
MLR			0.001
MLR0	73	21	
MLR1	52	18	
MLR2	67	34	
MLR3	114	68	

MLR = metastatic lymph node ratio.

*Log rank test.

Table 7. Geographical demographics

Variables	North-eastern India	South India	Central and North India	P-value
No. of patients	197 (46.1)	184 (43.0)	46 (10.7)	
Mean age (yr)	50.5	55	52.7	0.010
Location				0.634
Pyloro-antral	113	121	29	
Body	59	46	12	
Fundus	20	13	5	
Cardia	3	2		
Diffuse gastric cancer	2	2	0	
Staging				0.129
Stage I	21	21	4	
Stage II	39	43	16	
Stage III	137	120	26	
Male:female ratio	2.2:1	2.3:1	2.1:1	0.150
5-year OS (%)	66.0	52.0	59.0	0.238

OS = overall survival.

Sixty-one percent of tumors originated in the antro-pyloric region. Other reports from India also suggest distal tumors as more common than proximal tumors [4]. A large population based study from China revealed higher incidence of distal tumors [17]. However, in developed countries, there is a trend towards more proximal tumors [18].

In keeping with other reports from India, the majority of patients in our series presented at an advanced stage (stage III) [19]. A similar trend was seen in other regions where population-based cancer screening is not done such as America, Europe, and China [17,20,21].

The 5-year OS in our series is higher than from cancer registries in India. However, stage wise survival and DFS data for gastric cancer from India is lacking, thus comparisons are difficult. The Madras, Mumbai, and Bhopal cancer registry estimate the overall 5-year survival of gastric cancer (stage I–IV) at 8.0%, 15.0%, and 3.8%, respectively between 1990 and 2000 [2,22].

In comparison with international data, stage adjusted survival of operable gastric cancer from our series is similar to reports from the USA (MD Anderson group) and China. However, the stage adjusted survival data from Japan and South Korea exceed those reported in our series [17,20,23,24].

The subset analysis based on the geographical distribution of patients revealed that the stage wise distribution and location of tumor were comparable between patients referred from various parts of the country. Patients referred from the North-Eastern parts of the country presented 5 years earlier than those from the Southern part; they also had better 5-year DFS and OS. However, this did not translate into statistical significance. The exact reason behind this difference in survival is not known. India has a multi-ethnic population cohort as described by Basu et al. [25]. Difference in ethnicity between different populations in India along with different dietary habits may be attributed to this difference in age of presentation and survival. Further detailed studies to verify this observation are warranted.

The factors that predicted worse 5-year DFS and OS were analyzed. Poor tumor biology may be an unmodifiable factor. However, completeness of resection and performing aggressive surgery safely, including multi-visceral resections, may need to be explored given that R0 resection and adequate lymphadenectomy offer better survival rates [26].

There is little consensus on the management of Gastric cancer because of the 'East-West' divide. Over 50% of gastric cancer in a non-screened population such as Europe and America are inoperable or metastatic at presentation. There is a transatlantic divide in the management of gastric cancers. While chemo-radiotherapy is given in a perioperative setting in North America, neoadjuvant chemotherapy is given for locally advanced gastric cancer in the rest of the Western world. In contrast, over 50% of gastric cancers diagnosed in Korea and Japan are early stage and operated upfront irrespective of the stage of diagnosis. The OS is also vastly different between the East and the West (–60% vs. –20%, respectively) [27]. Given this global divide and heterogeneity of presentation, management, and outcomes internationally, it is imperative that Indian data is available to tailor the management of this disease to the Indian patient. This article aims to highlight the Indian experience with operable non-metastatic gastric cancer and to enhance the global perspectives on the long-term outcomes of this disease.

Most patients with operable gastric cancer present at an advanced stage in India. The 5-year DFS and OS of patients with non-metastatic gastric cancer treated at a dedicated upper gastrointestinal center in India is good and comparable with the results for other countries where no population-based screening is performed.

The study limitations are as follows, the study period spanned over 10 years, a period during which surgical technique, adjuvant therapy, and pathological definitions have changed. The mean follow up of 34.1 months is low. A majority of patients travelled more than 1,500 kilometers for therapy and follow-up, making complete and thorough follow-up logistically difficult. Moreover, because the study was performed at a single tertiary care center, a referral bias should be factored in the results

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