

**STUDY OF THE PATTERNS OF FAILURE IN
CARCINOMA ESOPHAGUS**



**A DISSERTATION SUBMITTED TO THE
TAMIL NADU DR MGR MEDICAL UNIVERSITY
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR
THE AWARD OF THE DEGREE OF
M. Ch (BRANCH VII) – SURGICAL ONCOLOGY**

CERTIFICATE

This is to certify that this dissertation titled “**STUDY OF THE PATTERNS OF FAILURE IN CARCINOMA ESOPHAGUS**” is a bonafide record of the work done by **Dr RATNAGIRI RANGANATH** in the Division of Surgical Oncology, under our guidance and supervision during the period of his post graduate study for M.Ch (Branch VII) Surgical Oncology from March 2004 to February 2007 in the College of Oncological Sciences, Cancer Institute (WIA), Chennai 20.

DR R RAVI KANNAN
PROFESSOR AND HEAD
DIVISION OF SURGICAL ONCOLOGY
CANCER INSTITUTE (WIA)
[GUIDE]

DR TG SAGAR
PRINCIPAL
COLLEGE OF ONCOLOGICAL SCIENCES
CANCER INSTITUTE (WIA)

DECLARATION

I hereby declare that this dissertation titled “**STUDY OF THE PATTERNS OF FAILURE IN CARCINOMA ESOPHAGUS**” has been prepared by me under the guidance of Dr R Ravi Kannan, Professor & Head, Division of Surgical Oncology, College of Oncological Sciences, Cancer Institute (WIA), Chennai 20, as part of my study for the award of Degree of M.Ch. (Branch VII) Surgical Oncology from 2004 to 2007 of the Tamil Nadu Dr. MGR Medical University. It has not been submitted previously for the award of any degree or diploma from any university.

Dr Ratnagiri Ranganath

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I humbly acknowledge the courage and fortitude of my patients and pray for their future well being.

Last but not the least, none of this would have been possible without the enormous support, technical knowledge and constructive criticism of my wife, Prajnya.

*“Surgeons must be very careful
When they take the knife
Underneath their fine incisions
Stirs the culprit –Life!”*

Emily Dickinson (1805-1886)

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Introduction

Carcinoma esophagus is the fifth most common malignancy world wide and occurs at a crude incidence rate of 5.5 per 100000 population ¹. It is unique among cancers of the gastrointestinal tract in that it traverses three anatomical compartments: the neck, thorax and the abdomen, and encompasses two different primary histologies: adenocarcinoma and squamous cell carcinoma.

Natural history data and patterns of failure after specific treatment modalities provide an insight into the biologic tendencies of esophageal malignancy and suggest potential therapeutic avenues to explore.

At presentation, the majority of patients have locally or regionally advanced or disseminated cancer, irrespective of histology ². The lack of a serosal envelope and the rich submucosal lymphatic network of the esophagus provide a favorable milieu for extensive local infiltration by the tumor as well as lymph node involvement. Even if distant disease is not apparent clinically or radiologically at presentation, studies suggest that micrometastases are invariably present. This is borne out by the high incidence of distant sites as a significant and universally fatal component of failure ³. Bone marrow samples from ribs obtained during thoracotomy for esophagectomy

were shown to be positive for tumor cells by immunohistochemistry and polymerase chain reaction (PCR) studies in up to 90% of the patients sampled ⁴. The clinical significance of these findings is not known, but probably indicates the need to focus on systemic therapy in addition to loco regional treatment.

Median survival after esophagectomy for patients with localized disease is 15 to 18 months with a 5-year overall survival rate ranging from 27 % to 30%. The patterns of failure are influenced by the site of the tumor and the histology. Loco regional recurrences predominate in tumors of the upper and middle third whereas distant failure is more common with adenocarcinomas arising in the lower esophagus ³.

The addition of chemotherapy, chemo radiotherapy or radiotherapy to surgery may alter patterns of failure but the reported results are not consistent. Incidence of distant metastases does not seem to be affected by any of these combinations, and thus improvement in survival rates will need a further stress on systemic modalities of therapy.

We attempt to study the patterns of failure in patients who have been treated with different treatment modalities, and also to possibly

delineate the natural history of the malignancy by means of a retrospective analysis of the data on these patients. We hope that this study would lead to further research in decreasing the morbidity associated with treatment and contribute to a better understanding of the biology of carcinoma esophagus.

Objectives

1. To study the patterns of failure in patients of carcinoma esophagus treated with various modalities.
2. To identify the treatment related morbidity and the means to reduce the same.
3. To study the feasibility and validity of the sentinel node concept in carcinoma esophagus.

Materials and
Methods

A total of 818 patients of carcinoma esophagus were seen in the outpatient department of our Institute during a ten year period from 1995-2004.

Of these 818 patients, only about 368 were considered suitable for some form of treatment after clinical assessment of the metastatic nature of the disease and performance status.

A retrospective review of the records of all these patients was done. Data for 346 patients was available in full and was considered for analysis.

Information regarding the demographic characteristics of the patient and the possible risk factors was collected.

In addition, the clinical symptomatology, physical findings and imaging characteristics were also looked at. The extent of the tumor as determined by esophagoscopy and in most cases, CT scan of the chest and abdomen was also assessed. The general condition of the patients, pulmonary reserve as measured by a pulmonary function test and most importantly, the willingness of the patient to undergo major surgery or radiation therapy were the criteria used in selecting patients for a particular treatment modality.

The treatment modality chosen, the complications because of the treatment given and the response of the tumor to therapy was also documented. In patients who underwent surgery, the approach chosen, the extent of lymphadenectomy and the pathologic tumor and nodal status were recorded.

The site of first failure and secondary treatment if given was also established.

Sentinel node biopsy:

The feasibility of a sentinel node biopsy was proposed to be prospectively examined in 6 patients of carcinoma esophagus. However, because of logistic reasons it could be done only in one patient. About 5 to 7 ml of patent blue dye was injected intra operatively, before mobilization of the esophagus was performed. As the diffusion of the dye would occur within two to three minutes, transmural injection of the dye into four quadrants at the level of the tumor was done.

The node or nodes which were stained blue were dissected out and the appropriate level colour coded on a chart. These nodes were sent separately for histopathologic examination. The rest of

the surgery was completed as per the pre operative plan with the requisite lymph node dissection. The non-sentinel nodes which were found to be metastatic were marked on the same chart with a different colour.

Statistical methods used:

The data was analysed using the SPSS software. Frequency tables were generated by the software and used to convert the data into relevant clinical conclusions. Kaplan Meier curves were used to assess the expected survival of the different subsets within the cohort. The Cox regression test was used to determine statistically significant factors which affected survival.

Review of
literature

Epidemiology and biologic factors

Carcinoma of the esophagus is the sixth leading cause of death from cancer worldwide ⁵. According to the Madras metropolitan tumor registry (MMTR), it is the fourth most common cancer in males and sixth most common in females. The crude incidence rate is 5.5 per 100000 men and 4.1 per 100000 women ¹. More than 90% of esophageal cancers are either squamous cell carcinomas or adenocarcinomas. Malignancies arising in the upper or mid thoracic esophagus are usually squamous cell carcinomas, whereas adenocarcinomas arise more commonly in the distal esophagus ⁶. The lifetime risk of esophageal cancer is 0.8% for men and 0.3 % for women, and increases with age with a mean age at diagnosis of 67 years ⁷.

Once cancer develops it may spread rapidly: 14 to 21% of T1 lesions and 38 to 60% of T2 tumors are associated with lymph node involvement ⁸. At the time of diagnosis, about 50% of patients have either unresectable tumors or radiographically visible metastases.

Although surgery is considered to be the mainstay of treatment of esophageal cancer, there are many factors which mitigate its

success. The esophagus lacks a serosa, and once the tumor penetrates the muscular layer, it can invade any of the surrounding structures. The submucosa is rich in lymphatics which spread longitudinally as well as laterally, and so submucosal spread of tumor especially proximally is common ⁹. The longitudinal network of lymphatics allows spread of the tumor to the neck, thorax and abdomen irrespective of the location of the tumor. Once a tumor has breached the muscular layer, the incidence of lymph node involvement exceeds 75% ⁹. Definitive therapy therefore should aim not only at loco regional control but also systemic control of disease.

Natural history

Carcinoma esophagus is often far advanced at the time of diagnosis and only a small number of patients are considered for curative therapy and possible long term survival. Resection rates vary from 19 to 64% and 5 year survivals from 10 to 55% depending on the stage of the cancer. Surgical resection remains the backbone of therapy as it provides sustained palliation of dysphagia and the best chance for cure ¹⁰. Advances in surgical and anesthetic techniques have contributed to a significant decrease in the post operative mortality.

This has however not been converted into survival benefit as patients present with recurrent disease following apparently curative surgery. Hence attempts have been made to improve the survival by increasing the radicality of the lymphadenectomy or by combining surgery with other treatment modalities. An understanding of the sites, causes and timing of the recurrences will therefore point us in the right direction of attempting to improve the survival of these patients.

Mariette et al detected loco regional recurrences in more than 50% of their patients who had undergone apparently curative esophagectomy within the first 3 years after surgery with an overall 5 year survival rate of 41%³. In their study distant failures were more common with malignancies of the lower third of the esophagus. Tumor depth appeared to be the only significant factor predictive of loco regional or distant failure.

The frequency of distant failures has been shown in a few studies to be almost the same as that of loco regional failure (37% v/s 39%), with almost the same median time to failure (11 months v/s 13 months). This suggests that micrometastases have already occurred

at the time of diagnosis and that these metastases grow more rapidly after the primary is resected ¹¹.

Some authors also believe that lymphatic and hematogenous metastases occur independent of each other, and this accounts for the distant failure in about 40% of patients who are lymph node negative ¹². One prospective study demonstrated an incidence of 88% micrometastases in the ribs and 15% in iliac bone marrow specimens of patients with localized carcinoma esophagus who underwent surgery ⁴.

Hence there are two groups of patients who need to be identified: one, those patients with metastatic disease which is not picked up by the current modalities of investigation and two, those with micrometastases. The former group can be excluded from curative treatment options whereas the second group needs to be enrolled in trials of systemic therapy.

Evolution of surgery for carcinoma esophagus

With reduced perioperative morbidity and mortality, surgery remains an effective modality, either alone or in combination with other

approaches, in providing local tumor control with durable relief of dysphagia, and the potential for a prolonged disease free survival.

Selection of the optimal approach depends on the tumor location, histology, extent of local resection and lymphadenectomy, anastomotic site, performance status and most importantly the surgeon's experience. No prospective trial has shown a survival advantage to any one approach ¹³.

Transhiatal esophagectomy (THE) entails mobilization and resection of the intra thoracic esophagus and limited nodal dissection through an abdominal and neck incision, without a thoracotomy. This procedure requires less operating time than the trans thoracic approach and avoids the complications of a thoracotomy. As initially described by Denk ¹⁴ and re introduced by Orringer and Sloan ¹⁵, this approach does not afford direct visualization of middle or proximal third tumors thus limiting the ability to perform a complete intra thoracic lymphadenectomy and increasing the potential for injury to the intra thoracic structures. Reported survival rates range from 22% to 27%.

Transthoracic esophagectomy (TTE) involves resection of the esophagus and associated lymphatic tissue and is performed through

a thoracotomy and laparotomy incision. Upper and mid thoracic lesions are approached through a right thoracotomy whereas lower esophageal cancers can be approached through the left side. Initially described by Lewis ¹⁶ in 1946, this technique offers excellent exposure and theoretically allows for a more definitive oncologic procedure. The three incision approach of McKeown ¹⁷ with a cervical incision, right thoracotomy and laparotomy combines the advantages of a cervical anastomosis with the exposure of an Ivor- Lewis procedure. The most common post operative complications include respiratory compromise (atelectasis, pneumonia and empyema); anastomotic leak with mediastinitis and wound infections ¹⁸.

En bloc esophagectomy was initially proposed by Logan in 1963 and modified by Skinner in 1969 ¹⁹. It entails en bloc resection of the thoracic esophagus with the azygous vein, thoracic duct, mediastinal pleura and pericardium through a thoracotomy. Local recurrence rates are less than 10% and when compared to limited resections, en bloc esophagectomy has provided improved survival ²⁰.

Two large reviews comparing transhiatal (THE) and transthoracic esophagectomy (TTE) have been published. Both reviews found a

significantly higher operative mortality among patients resected by TTE (9.5% v/s 6.3%). A higher anastomotic leak rate was reported for THE; however, when a leak occurred in a patient who had undergone trans thoracic esophagectomy, the mortality was much higher because of the associated mediastinitis. Recurrent laryngeal nerve palsy was found to be higher with the transthoracic approach. Cancer related survival appeared to be the same with both approaches ^{21, 22}

A standard lymphadenectomy involves the removal of the periesophageal and perigastric nodes. In addition to a thorough mediastinal dissection extending from the carina to the hiatus, an upper abdominal dissection along the hepatoduodenal ligament, celiac axis, left gastric and splenic arteries is accomplished in a **two-field lymph node dissection** ²³. A **three-field lymphadenectomy** extends the dissection to the superior mediastinum including nodes along the right and left recurrent laryngeal nerves and through a separate collar incision in the neck, completes the dissection with removal of the lower cervical nodes ²⁴. Altorki et al reviewed a series of patients who underwent three field dissection, with a post operative mortality of 5.1% and a respiratory complication rate of 24%. The 4 year survival was 41.5% which was significantly better than the

standard resection group ²⁵. A group at Cornell University examined 80 patients who underwent three field lymphadenectomy. Over all 30 day mortality was 5% with a respiratory complication rate of 16%, anastomotic leak rate of 11% and a 9% incidence of recurrent laryngeal nerve palsy. Over all 5 year survival was 51%. The incidence of cervical nodal metastases was about 36% and the survival in this sub group was only 25% ²⁶.

Radiation therapy (RT) and ChemoRT in the treatment of carcinoma esophagus

Several large randomized trials have been conducted to explore issues relating to the multi modality treatment of esophageal cancer. Unfortunately, however, the standard of care remains controversial. Kelsen et al reported the results of an Intergroup trial for 440 patients with potentially resectable carcinoma of the esophagus. Patients were randomized to surgery alone or preoperative chemotherapy followed by surgery. Those patients whose disease was responsive or stable received post operative chemotherapy. Only about 52% of the patients eligible to receive post operative chemotherapy actually did so. The median survival of patients treated with preoperative

chemotherapy was 14.9 months and for those treated with surgery was 16.1 months²⁷.

Clark et al demonstrated a survival of 16.8 months for patients who received pre operative chemotherapy when compared to 13.3 months for patients who did not²⁸.

There have been numerous trials of chemoradiation versus surgery. Walsh et al reported the results of an Irish trial in which patients were treated with surgery or preoperative chemoradiation. Median survival was 16 versus 11 months in favor of the chemoradiation arm²⁹.

The EORTC (European Organisation for Research and Treatment of Cancer) conducted a multi center trial comparing preoperative chemoradiation to surgery alone in patients with Stage I and II squamous cell carcinoma. There was no survival difference between the two arms with a median survival of 18.6 months and a 3 year survival of 36%³⁰.

Urba et al were also unable to demonstrate any significant survival advantage for chemoradiation³¹.

A multi institutional trial headed by RTOG (Radiation Therapy Oncology Group) was reported in 1992 comparing patients who were

randomized to receive treatment with radiation alone versus those who received radiation with two courses of concurrent chemotherapy followed by two more courses of chemotherapy. The median survival was 14.1 months and 5 year survival was 27% in the chemoradiation arm; median survival was 9.3 months with no patients alive at 5 years in the radiation alone arm ³².

Hence, surgery remains the standard of care for patients with resectable disease. Definitive chemoradiation is the treatment of choice for patients considered unfit for surgery. There is no definitive evidence that chemoradiation plus surgery is superior to surgery alone.

Role of sentinel node biopsy in carcinoma esophagus

In the surgical management of carcinoma esophagus, radical lymph node dissection has played a significant role in the twentieth century. Survival benefit of three field lymphadenectomy for esophageal cancer has been shown by Japanese researchers ²⁴. The feasibility of radical lymphadenectomy and the demonstration of a convincing survival benefit in the face of the considerable morbidity is still an issue in the Western world. Secondly, completion of radical lymphadenectomy in minimally invasive procedures is still difficult.

Therefore, determination of optimal extent of lymph node dissection based on actual node status is required. A sentinel node sampling is a step in this direction.

A sentinel node is defined as the first draining node from the primary lesion and the first possible site of metastasis ³³. Orderly progression of lymph node metastases has been well documented in breast cancer and melanoma. The validity of the sentinel node concept for gastro intestinal cancers has not however been verified.

Kitagawa et al described their technique of detection of sentinel nodes in carcinoma esophagus using radioactive technetium 99m- tin colloid. The tracer was injected sub mucosally through an endoscope at the site of the tumor about seven hours prior to surgery, and a hand held gamma probe was used intra operatively to localize the sentinel node. Sentinel nodes were located in the first nodal basin based on anatomic classification only in 15% of the patients. The detection rate was 91% with a sensitivity of 86% ³⁴.

Burian et al reported an 85% detection of sentinel lymph nodes in adenocarcinomas of the lower esophagus with a specificity of 75%. They used a combination of blue dye and radio tracer ³⁵.

In a study by Kato et al, the sensitivity of the sentinel node procedure was 86.7% and the false negative rate was 8.7%. Occult metastasis was detected by cytokeratin staining in 1.7% of the lymph nodes ³⁶.

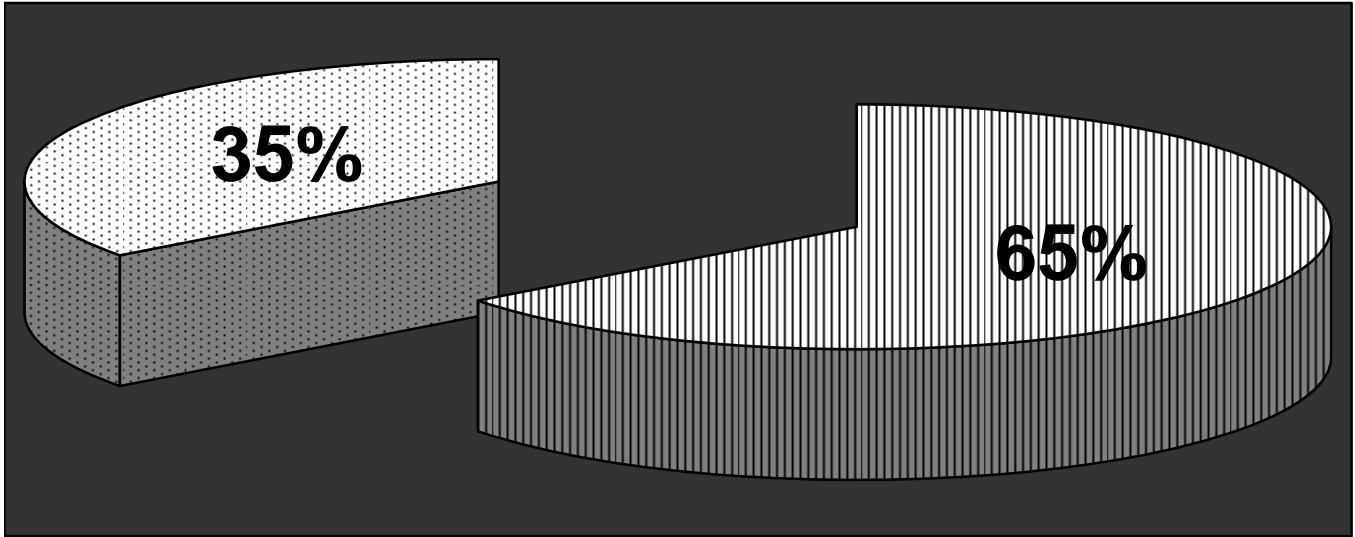
These studies show that the sentinel node concept is valid even for upper gastro intestinal cancers with multi directional and complicated lymphatic flow. The relatively high incidence of anatomic skip metastases can be attributed to the aberrant distribution of the sentinel lymph nodes. An individualized and minimally invasive surgical approach can be applied to the management of esophageal carcinoma based on the sentinel node status.

Results

Table 1: Demographic profile: Age wise distribution (N=346)

Age group	Number	Percentage
<30 years	14	4.0
31-39 years	59	17.0
40-49 years	88	25.4
50-59 years	109	31.5
60-69 years	64	18.5
>70 years	12	3.5
Total	346	100

Figure 1: Gender wise distribution



As the above data shows, about 65% of the patients were male and about one third belonged to the sixth decade.

**Table 2: Clinical features – symptomatology
(N=346)**

SYMPTOM	NUMBER	PERCENTAGE
Dysphagia	335	96.8
Chest pain	10	2.9
Hoarseness	1	0.3
Total	346	100

**Table 3: Risk factor- smoking
(N=346)**

SMOKING	NUMBER	PERCENTAGE
Yes	189	54.6
No	157	45.4
Total	346	100

**Table 4: Risk factor- alcohol intake
(N=346)**

ALCOHOL	NUMBER	PERCENTAGE
Yes	79	22.8
No	267	77.2
Total	346	100

**Table 5: Risk factor- family history
(N=346)**

FAMILY HISTORY	NUMBER	PERCENTAGE
Present	37	10.7
Absent	309	89.3
Total	346	100

Dysphagia was the most common presenting symptom and about 55% were long term smokers. Alcoholism and family history were present only in a few of the patients

Table 6: Tumor profile according to histology and site

	SQUAMOUS CELL CARCINOMA	ADENO CARCINOMA	BARRETT'S	GIST ¹	TOTAL
Cervical esophagus	16	0	0	0	16
Upper third	41	0	0	0	41
Middle third	199	4	0	0	203
Lower third	66	18	1	1	86

¹ Gastrointestinal stromal tumor

Squamous cell carcinoma was the most common histology constituting 92.7% of all the tumors. The mid thoracic esophagus was the commonest site (58.6%).

**Table 7: Primary treatment offered
(N=346)**

MODALITY	NUMBER	PERCENTAGE
RT ¹	183	52.9
Chemo RT ²	44	12.7
Surgery	108	31.2
Supportive care	11	3.2
Total	346	100

¹ External beam radiation therapy 6500 cGy

² Concurrent chemoradiation with cisplatin and 5 FU

31% were considered suitable for surgery on the basis of their performance status, staging investigations and pulmonary reserve. 75.6% of patients were treated either with radiotherapy alone or with concurrent chemo radiotherapy depending on their performance status and intent of treatment. 11 patients were initially considered suitable for treatment but on re evaluation were either found to have metastatic disease or poor general condition unsuitable for any form of therapy.

**Table 8: Response to RT
(n=183)**

RESPONSE	NUMBER	PERCENTAGE
No response	10	5.4
Partial response	50	27.3
Complete response	123	67.2
Total	183	100

Nearly 70% of the patients who were treated with radiotherapy or chemo radiotherapy achieved a complete response of the primary tumor as assessed by endoscopy and symptomatic relief.

**Table 9: Type of surgery performed
(n=108)**

SURGERY	NUMBER	PERCENTAGE
Trans hiatal	54	50
Two field	11	10.1
Trans thoracic	24	22.2
Inoperable	19	17.6
Total	108	100

As mentioned earlier, about 108 patients were taken up for surgery. 19 of these patients were found to be inoperable either due to peri esophageal extension of the tumor infiltrating the lefty main bronchus or aorta or due to dissemination in the form of liver metastases or peritoneal deposits. The site of the lesion and the performance status were used to decide the surgical approach.

**Table 10: Major complications of surgery
(n=89)**

SURGERY (N)	ANASTOMOTIC LEAK (%)	RIGHT RLN ¹ PALSY (%)	LEFT RLN PALSY (%)
Trans hiatal (54)	15(27.7%)	1(1.8%)	8(14.8%)
Two field (11)	1(9.1%)	0	0
Trans thoracic (24)	10(41.6%)	2(8.3%)	10(40.1%)

¹ Recurrent laryngeal nerve

Anastomotic leak and recurrent laryngeal nerve palsy were the two most common complications of surgery which led to increased morbidity. About 41% of patients who underwent trans thoracic esophagectomy had a leak and almost half (48.4%) of them had recurrent laryngeal nerve palsy.

Table 11: Status of the cohort as of June 2006 (N=346)

STATUS	NUMBER	PERCENTAGE
Alive; NED ¹	76	22.0
Alive with disease	1	0.3
Dead of disease	191	55.2
Dead unknown cause	65	18.8
Dead of treatment complications	5	1.4
Lost to follow up	8	2.3
Total	346	100

¹ No evident disease

The follow up of these patients ranged from 5 months to 134 months with a median of 66 months. 8 patients (2.3%) were lost to follow up. Out of the 346 patients on whom data is available, 76 (22%) are alive with no evidence of disease. 1 patient has been detected to have mediastinal recurrence and is alive.

**Table 12: Sites of failure in the cohort
(n=338)**

FAILURE SITE	NUMBER	PERCENTAGE
NED ¹	76	22.5
Esophagus	148	43.7
Mediastinum	8	2.3
Neck nodes	15	4.4
Liver	9	2.6
Peritoneal deposits	6	1.7
Skeletal metastases	5	1.4
Brain metastases	1	0.3
Pulmonary metastases	2	0.6
Skin nodules	1	0.3
Second primary	3	0.9
Unknown	64	18.9
Total	338	100

¹No evident disease

Irrespective of the histology and treatment modality chosen, the esophagus remained the most common site of failure followed by a percentage of patients in whom the failure site could not be documented. The supraclavicular nodes were the next common site of failure.

**Table 13: Correlation between histology and site of failure
(n=198)**

FAILURE SITE	SQUAMOUS CELL CARCINOMA (%)	ADENO CARCINOMA(%)	TOTAL
Esophagus	145 (73.2)	3 (1.5)	148
Mediastinum	6 (3.0)	2 (1.0)	8
Neck nodes	11 (5.5)	4 (2.0)	15
Liver	8 (4.0)	1 (0.5)	9
Peritoneal deposits	3 (1.5)	3 (1.5)	6
Skeletal metastases	5 (2.5)	0	5
Brain metastases	1 (0.5)	0	1
Pulmonary metastases	2 (1.0)	0	2
Skin nodules	1 (0.5)	0	1
Second primary	3 (1.5)	0	3
Total	185	13	198

Table 14: Correlation between primary treatment and site of failure (n=271)

FAILURE SITE	RT ¹	CHEMO RT ²	SURGERY	TOTAL (N)
NED ³	19	11	46	76
Esophagus	115	16	17	148
Mediastinum	1	1	6	8
Neck nodes	6	3	6	15
Liver	2	3	4	9
Peritoneal deposits	0	0	6	6
Skeletal metastases	5	0	0	5
Brain metastases	1	0	0	1
Pulmonary metastases	1	0	1	2
Skin nodules	1	0	0	1

¹ External beam radiotherapy

² Concurrent chemo radiotherapy

³ No evident disease

Table 15: Correlation between primary treatment and present status (N=346)

PRESENT STATUS	RT ¹ (%)	CHEMO RT ² (%)	SURGERY (%)	SUPPORTIVE CARE (%)
Alive; NED	19 (10.4)	11 (25)	46 (42.6)	0
Alive with disease	0	0	1 (0.9)	0
Dead of disease	121 (66.1)	21 (47.7)	42 (38.8)	7 (63.6)
Dead unknown cause	41 (22.4)	10 (22.7)	14 (12.9)	0
Dead of treatment complications	2 (1.1)	2 (4.5)	1 (0.9)	0
Total	183	44	108	11 ^a

^a Data unavailable for 4 patients in this group

¹ External beam radiation therapy

² Concurrent chemo radiotherapy

Table 16: Correlation between pathologic tumor stage and present status (n=94)

STATUS	T1 (%)	T2 (%)	T3 (%)	T4 (%)
Alive; NED	1(100)	14(77.7)	28(46.6)	2(13.3)
Alive with disease	0	0	1 (1.6)	0
Dead of disease	0	2 (11.1)	20(33.4)	12 (80)
Dead unknown cause	0	2 (11.1)	10(16.7)	1(6.7)
Dead of treatment Complications	0	0	1 (1.6)	0
Total	1	18	60	15

A greater percentage of patients with pT2 tumors (78%) were alive when compared to pT3 (48%) and pT4 (13%) tumors.

Table 17: Correlation between pathologic nodal status and present status (n=91)

STATUS	N0 ¹ (%)	RLN ² (%)	PERI ESOPHAGEAL (%)	PERI GASTRIC (%)
Alive; NED	26 (59.1)	5 (41.7)	13 (43.3)	2 (40)
Alive with Disease	1 (2.2)	0	0	0
Dead of disease	9 (19.8)	5 (41.7)	12 (40)	3 (60)
Dead unknown cause	7 (15.4)	2 (16.6)	5 (16.6)	0
Dead of treatment complications	1 (2.2)	0	0	0
Total	44	12	30	5

¹ Node negative

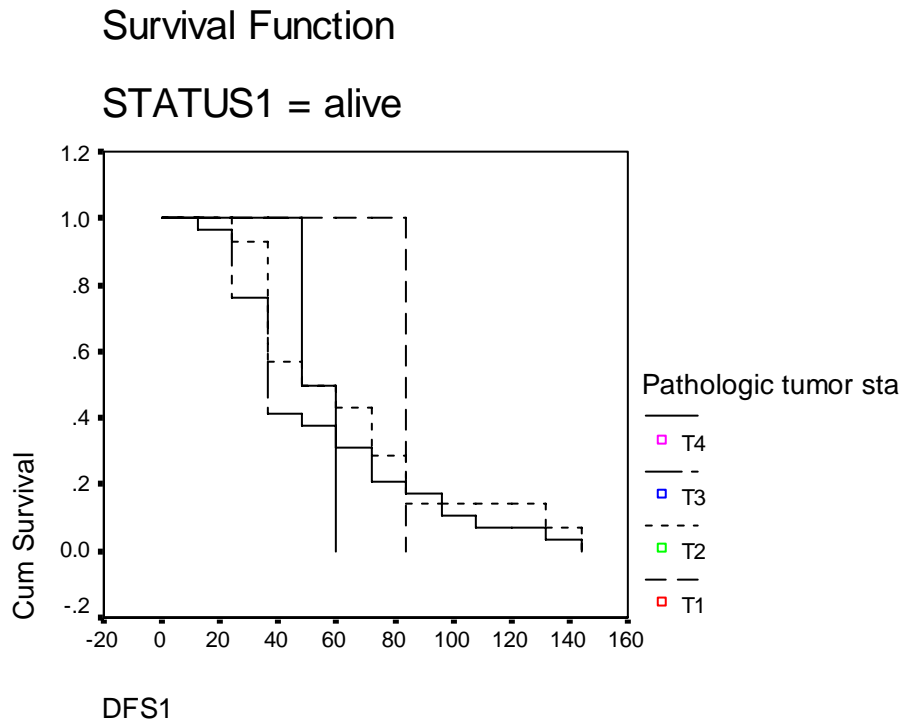
² Nodes along the recurrent laryngeal nerves and paratracheal nodes

Table 18: Correlation between perinodal spread of tumor and present status (n=88)

STATUS	ABSENT (%)	PRESENT (%)
Alive; NED	39 (57.3)	6 (35)
Alive with disease	1 (1.4)	0
Dead of disease	16 (23.5)	11(55)
Dead unknown cause	11 (16.1)	2 (10)
Dead of treatment complications	1 (1.4)	0
Total	68	20

Most patients with metastatic nodes were dead with no significant difference found between positivity of recurrent laryngeal and peri esophageal nodes (58.3% v/s 56.6%). However 65% of patients with perinodal spread were dead when compared to 39.6% of patients who did not have perinodal extension.

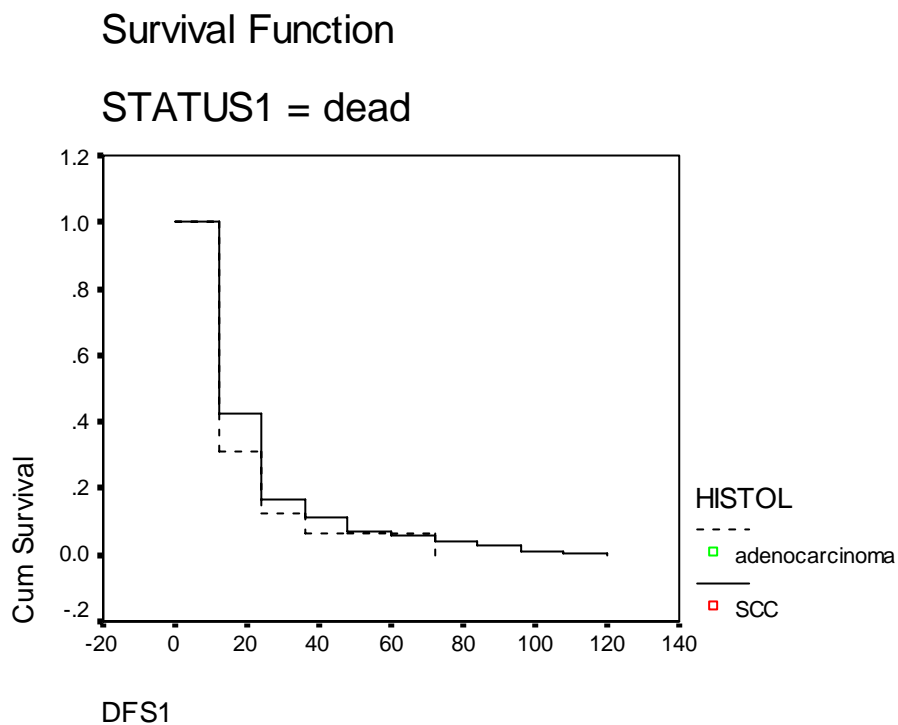
Figure 2: Factors influencing survival – pathologic tumor status (univariate analysis)



DFS – disease free survival in months

The median survival for patients with pT2 tumors was found to be 48 months, whereas that for pT3 was about 18 months to yield a p value of 0.05 on univariate analysis.

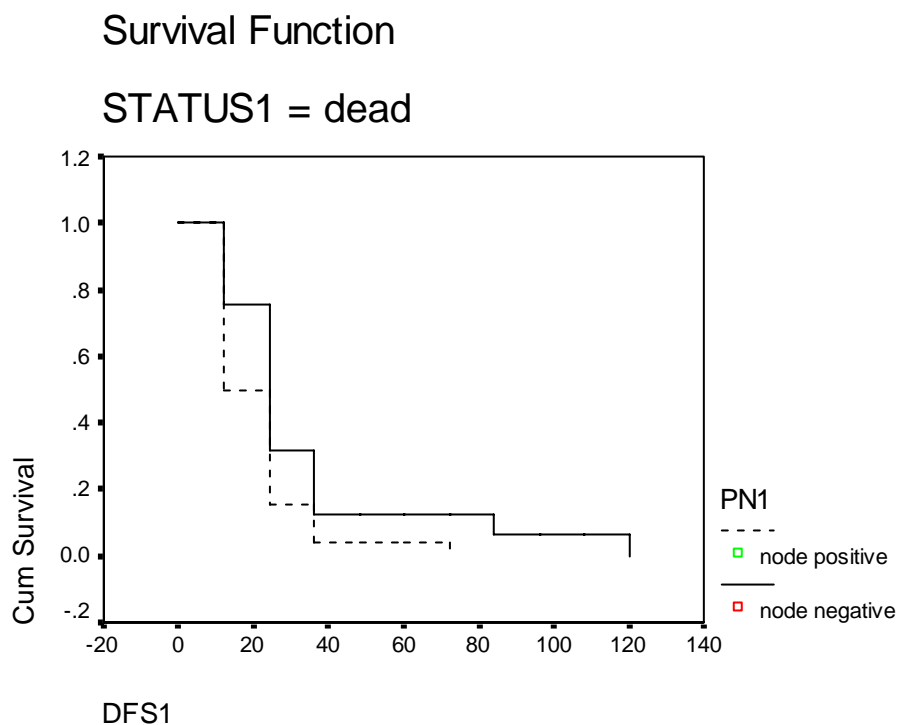
Figure 3: Factors influencing survival – histology (univariate analysis)



DFS – disease free survival in months.

There was no significant survival difference between the histologic variants of the esophageal tumor.

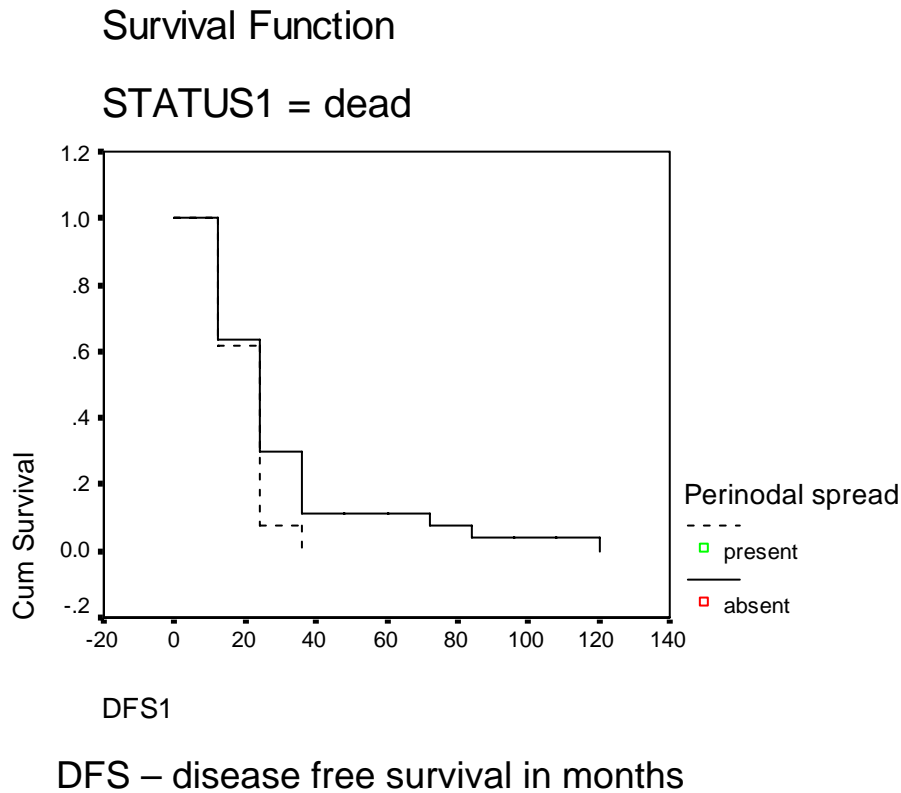
Figure 4: Factors influencing survival – Nodal status (univariate analysis)



DFS – disease free survival in months

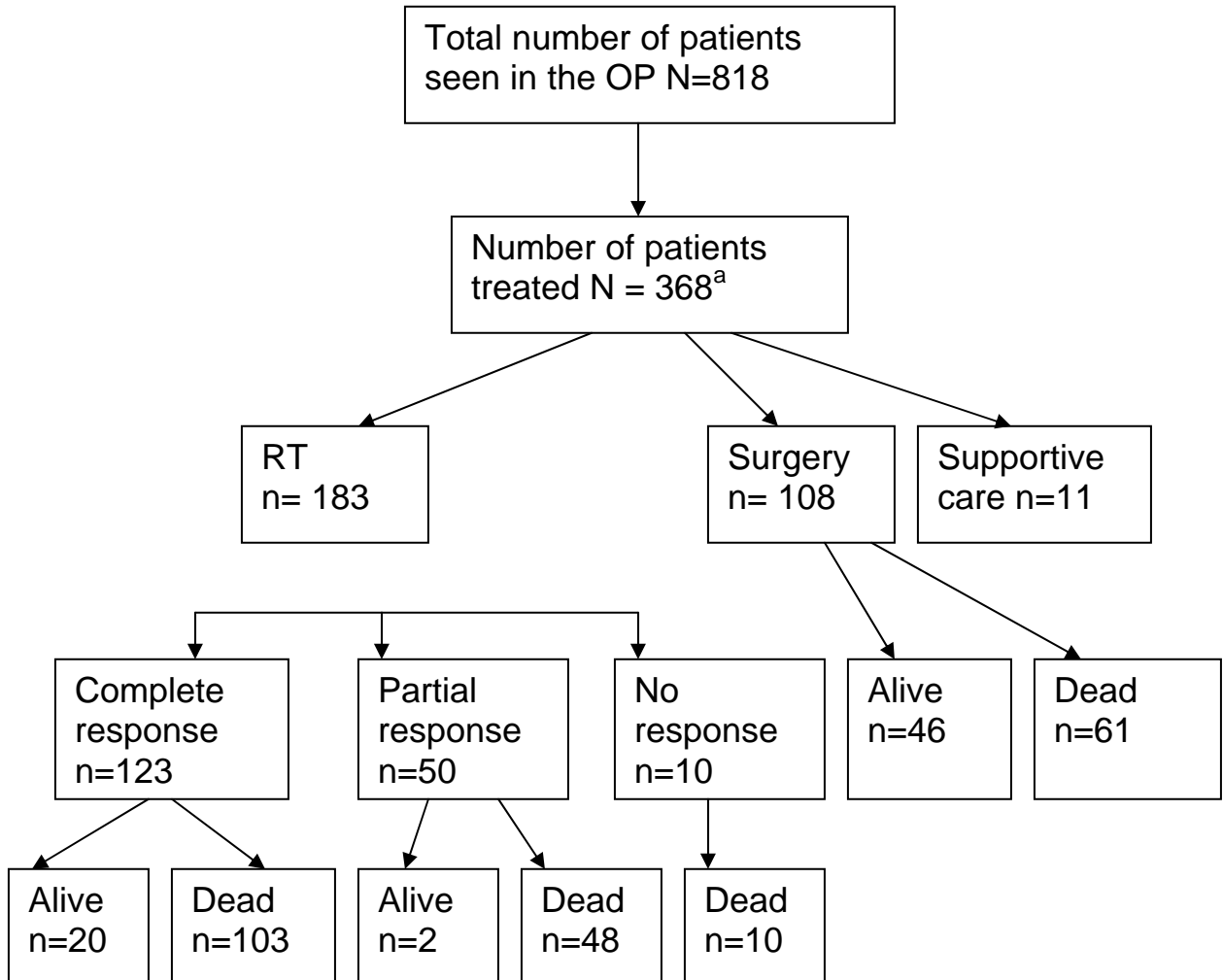
The median survival of node negative patients was 50 months whereas that for node positive patients was 31 months only ($p < 0.05$).

Figure 5: Factors influencing survival – perinodal spread (univariate analysis)



In patients with nodal positivity, those with perinodal spread had a median survival of only about 24 months, whereas those without perinodal spread had a median survival of 32 months ($p=0.05$).

Figure 6: Summary of the study



^a Data available for 346 patients.

Discussion

Esophageal cancer is a malignancy where refinements of surgical technique and the evolution of more radical procedures have not resulted in a proportionate increase in survival. As surgeons become more radical in their approach, the morbidity of the procedures increases and the quality of life of the patients decreases. Hence the thrust of future research will be on minimally invasive surgery, tailoring the nodal dissection according to the nodal status and newer adjuvant and neo adjuvant therapies.

The age and gender distribution of our cohort roughly parallels that of other studies and the report of the IARC (International Association for Research against Cancer)^{1, 2}. Most patients are male and the single largest group belonged to the sixth decade. Also these males who developed esophageal cancer were long term smokers (55%), but the consumption of alcohol (22%) was surprisingly low in contrast to other reports on the etiology of esophageal malignancy⁷.

Most patients who presented to the out patient department of our Institute were found to have metastatic disease at presentation or were found to have too poor a performance status to be considered for any kind of therapy. Consequently, of the 818 patients of esophageal cancer seen during the period of study, only about 368

(45%) patients were accepted for treatment. Studies by Pisani et al and data from the National Cancer Institute reflect the same trend wherein about 50% of newly diagnosed patients of esophageal cancer are found to be unsuitable for definitive treatment either due to metastatic disease or due to loco regionally advanced tumors^{5,7}.

Patients were considered good candidates for surgery on the basis of their performance status (0 or 1) and an objective assessment of their pulmonary function. Those patients who were not willing to undergo surgery were offered radiation therapy or concurrent chemo radiotherapy. As the data covers the period between 1995 and 2004, and the benefit of concurrent chemo radiotherapy had not yet been convincingly demonstrated in the earlier half of the study period, there is a relatively smaller number of patients (12.7%) in the concurrent chemo radiotherapy group.

Primary therapy for esophageal cancer is either surgical or non surgical. For several reasons this results in a selection bias against non surgical therapy. First, patients with unfavorable prognostic features are selected for treatment with non surgical methods. Second, surgical series report results based on pathologic staging whereas non surgical series rely on clinical and radiologic staging.

Third, because some patients treated without surgery are approached with a palliative intent, sub optimal doses of radiation or chemotherapy may have been used.

Many studies have reported results using external beam radiation therapy alone. Most include patients with unfavorable features like T4 disease and multiple positive nodes. The use of radiation as a potentially curative modality requires doses of at least 5000 c GY at 180 to 200 c GY per fraction. Shi and colleagues reported a 33% 5 year survival rate with the use of accelerated fractionation to a total dose of 68.4 Gy³⁷. However, in the radiation therapy alone arm of the RTOG 85-01 trial (Radiation Therapy Oncology Group), all patients were dead of disease by three years³².

Our data has a higher percentage of patients with complete response to RT (70%), but the 5 year survival is a dismal 13%. This can be explained by the fact that the response to treatment was assessed by endoscopy alone and hence there may not have been pathologic complete response in the majority of these patients. None of the patients received radiation therapy or concurrent chemo radiotherapy as neoadjuvant therapy and none of the patients who had a residue after therapy were considered for surgery.

Though only a small number of patients were treated with concurrent chemo radiation therapy (44), the 5 year survival of this group (25%) correlates well with the results of Herskovic et al(5 year survival of 27%)³².

The nature of surgery offered was decided by the site of the tumor, loco regional extent, the performance status and the pulmonary function. More than 50% of the patients underwent a trans hiatal esophagectomy, with trans thoracic esophagectomy being performed in 22%.

Hulscher et al randomized patients into two surgical arms: trans hiatal versus trans thoracic. They found that the ICU stay and the hospital stay in the post operative period was significantly more in the trans thoracic group. However, the 5 year overall survival between the two arms was not significantly different (29% versus 39%)³⁸.

The two most common complications in our study which led to increased hospital stay were anastomotic leak and recurrent laryngeal nerve palsy. Our documented leak rate was 28% in the trans hiatal group and about 41% in the trans thoracic group. Recurrent laryngeal nerve palsy was found in 14% of patients who

underwent a trans hiatal esophagectomy and in 40% of patients who underwent a trans thoracic esophagectomy.

These percentages are much higher than the published rates of 10-15% of anastomotic leak and about 12-14% recurrent nerve injury in various studies, and can only be attributed to the surgeons' learning curve.

In spite of the higher incidence of post operative morbidity compared to other published studies, the 5 year overall survival of the surgical arm of the study population is about 42%, which compares well with the best of studies.

A study published by the MD Anderson Cancer Center attempted to determine the difference in natural history and prognosis between squamous cell carcinoma and adenocarcinoma of the esophagus. They found that the incidence of nodal spread and distant metastases was slightly higher in patients with adenocarcinoma. However, the disease free survival and the overall survival was the same in both groups³⁹.

This is reflected in our data which show no significant survival difference between the two major histologic variants.

Mariette et al pointed out that in their study the only factor which predicted disease recurrence and survival was the pathologic tumor status. However they were unable to demonstrate the effect of nodal positivity on survival ³. Tabira et al in their study of patients who underwent trans thoracic esophagectomy determined age, T4 tumors and number of metastatic nodes as the factors which influenced survival ⁴⁰.

In our study, pathologic tumor status, nodal positivity and peri nodal spread were the factors which affected survival on univariate analysis. However, on multivariate analysis, only peri nodal status seemed to be statistically significant.

The esophagus, mediastinum and the supra clavicular nodes were the most common sites of failure irrespective of the histology and the treatment modality.

Dresner et al reported a 21% local recurrence rate following a radical esophagectomy, which is much lower than that reported in series where no formal lymphadenectomy has been done. However, some node positive patients had a 5 year survival of 39%, which confounds the influence of nodal dissection on survival. This probably can be

explained by the absence of peri nodal spread conferring a relative survival advantage in this subset of patients ⁴¹.

The demonstration of an improvement in survival of patients who underwent three field lymphadenectomy by Japanese surgeons needs to be carefully balanced by the additional morbidity of increased vocal cord paralysis.

A *via media* between the radicality of a three field lymphadenectomy and the inadequate lymph node dissection of trans hiatal esophagectomy is the sentinel node biopsy procedure. Further oncologic research needs to focus on this aspect along with newer modalities of adjuvant/ neo adjuvant therapy in the attempt to improve survival in esophageal cancer.

Summary and
conclusions

A total of 818 patients of carcinoma esophagus were seen in the out patient department of our Institute in the period 1995-2004.

Of these, about 368 patients (44.9%) were offered treatment of some kind.

65% of these patients were male and about 31.5% belonged to the sixth decade.

About 97% of the cohort presented with dysphagia.

55% of the patients were smokers whereas only about 23% gave history of long term alcohol intake.

52.6% of all tumors were located in the mid thoracic esophagus and 92.7% of all tumors were squamous cell carcinomas.

31.2% of the cohort were considered suitable for surgery.

Of the 227 patients who were offered radiotherapy or chemo radiotherapy, 157 (69.1%) had a complete response.

Only 13.2% of the patients treated with radiation therapy were alive at 5 years.

129 patients (82.1%) of those who had a complete response were dead at 5 years.

108 patients underwent surgery, of which 54 (50%) were trans hiatal esophagectomies.

28% of the patients who underwent trans hiatal esophagectomy and 41% of the patients in the trans thoracic esophagectomy group developed an anastomotic leak.

14% of the patients in the trans hiatal group and 41% of the trans thoracic group had vocal cord palsy.

26.7% of the patients in the surgery arm developed loco regional recurrences. Most of these recurrences were in the first three years after the surgery.

About 42.6% of the surgery arm as a whole was alive at 5 years.

78% of patients with pT2 tumors were alive at 5 years when compared to 48% of patients with pT3 tumors and 13% of pT4 tumors.

The median survival of patients with node negative disease was 50 months whereas that of node positive patients was 31 months.

65% of patients with perinodal spread of tumor were dead at 5 years.

This retrospective study of 346 patients of esophageal cancer demonstrates the dismal survival rates achieved with radiation therapy alone, which seem to be improved dramatically with the addition of concurrent chemotherapy. No definitive claims can be

made on this front however, in view of the small number of patients administered chemoradiation therapy. There was a high rate of complications with the surgical arm, though the 5 year survival achieved approximated the best in available literature. Pathologic tumor stage, nodal positivity and peri nodal spread were found to be prognostic on univariate analysis, however only peri nodal extension of tumor was the only factor found to be statistically significant on multivariate analysis. Hence a balance needs to be struck between the survival benefit of extended lymph node dissections and the consequent complications. Sentinel node biopsy offers a simple and efficient means of achieving this and further research should be in this direction.

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