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Outcome of Oesophageal Cancer Treatment at a National Hospital, from 2015 to 2017

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Abstract

Background

Oesophageal cancer is among the most common cancers in Tanzania. Patients usually, unfortunately, come to medical care with advanced disease and for this reason, despite advancement in treatment of cancer and multidisciplinary treatment approaches (surgery and chemoradiotherapy), Oesophageal cancer still has a 5-year survival rate of less than 20% and high rate of recurrence after initial treatments. Here in Dar es Salaam, we studied the outcomes of treatment in these cases to have an estimation of the general prognosis of patients and have a general picture of the treatment modalities and outcomes.

Methods

In this retrospective study we reviewed data of patients which included cancer stage at diagnosis, types of treatments and their treatment outcomes. This involved data from patients who were admitted from January 2015 to December 2017. The total period of survival recorded was taken up to 2yrs from the date of onset of treatment. This study was done in Muhimbili National hospital and Ocean Road Cancer Institute, both located in Dar es Salaam, Tanzania.

Results

The Study included 128 patients of which 77(60.2%) were males with a general median age of 55.9 years (range: 20 years to 91 years). Majority of the patients were diagnosed at an advanced stage of the disease. Stage III or IV was observed in 82.5% (106/128) of patients with Oesophageal cancer, rendering them to get only palliative therapy (79%). The overall 2-year survival rate was 8%, and the mean duration for local recurrence was 3.6 ± 1.2 months. Late diagnosis was the main factor for poor outcomes and hence low 2-year survival rate.

Conclusion and recommendation

Oesophageal cancer has higher mortality and shorter survival period because it is diagnosed very late. The treatment offered, therefore, at this stage is usually palliative which doesn't alter the dismal course of the disease. More efforts are needed to sensitize the general population to seek consultation for early diagnosis and treatment.

Keywords: *Oesophageal cancer survival, Dysphagia grade, Treatment outcome, Cancer recurrence.*

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Background

Oesophageal Cancer is the seventh commonly occurring Cancer and sixth most common cause of death in the world (1) with a 5-year survival rate of 18.8% (2). The disease has a geographical distribution having high incidence in Eastern Asia and Southern and Eastern Africa. Tanzania ranks 12th among countries with the highest rate in the world (2). Treatment of oesophageal cancer varies according to the stage of the disease; loco-regional (stages I to III) versus metastatic cancer, and histological subtypes (that is squamous cell carcinoma versus adenocarcinoma). Treatment options of the disease include surgery (esophagectomy, commonly used procedure), chemotherapy, radiotherapy as well as palliation. Chemotherapy and radiotherapy can be offered as preoperative, postoperative, definitive management or as palliation (3).

In most studies, surgery has a better outcome than chemoradiotherapy. It has a high survival rate and a low recurrence rate (4, 5). However, combining the approaches (Chemoradiotherapy (both preoperatively and postoperatively) and surgery) is associated with good outcomes in terms of mortality, survival rate, and low-rate of disease recurrence, compared to patients who receive either chemoradiotherapy or surgery alone (6). Mortality rate of the disease after treatment can also be contributed to some extent by the treatment complications of the disease, particularly in the old population. Surgical complications tend to be within a short time and more serious than chemoradiotherapy since surgery is an invasive procedure (7).

In cases of inoperable disease which is the characteristic of most patients in Tanzania where about 90% of cancer cases are diagnosed in late stages (8), most patients have stage IV disease. When these patients present to the hospital, they have a very low survival rate after palliative care despite the fact that they get significant improvement in dysphagia grade following palliative dilatation or stenting. Furthermore, there are published studies that assess the survival rate of this disease in Tanzania hospitals (9).

This study was carried out to primarily determine the 2-year survival rate and degree of dysphagia four weeks post treatment. We also wanted to know about the duration time that it takes for the disease to recur. This kind of information would therefore add information to the prevailing body of knowledge and data will be used in advocating the use of huge investments in both skills and technological equipment required in oesophageal cancer treatment interventions in order to decrease the poor outcomes from treatments offered.

Information gathered from this report will also lead to significant likelihood of the vulnerable people and the community at large to adapt behaviors that enhance early health seeking and reporting of symptoms to the appropriate centers. The findings of this study have considerable policy implications on the country's health system. This includes a focus on those factors that increase individual vulnerability and poor outcome from various treatment modalities offered at different health centers and ensure that dysphagia patients are adequately protected by getting them early enough and giving them timely appropriate treatment. This goes in parallel with regular assessment of the implementation of the policies that have been developed.

Methodology

A retrospective study design carried out at Muhimbili National Hospital (MNH) and Ocean Road Cancer Institute (ORCI) was done. MNH is a National and tertiary hospital that receives patients with various conditions such as oesophageal cancer who, following a history of dysphagia for diagnostic work up and, may need surgery (oesophagectomy), patients who need palliative initial treatment such as Oesophageal stenting and/ or gastrostomy feeding tube before being sent for chemoradiotherapy. ORCI receives patients who need chemoradiotherapy as neoadjuvant, palliative or adjuvant treatment directly from referral hospitals in the country or from MNH after diagnostic work up. Since the disease needs multimodal therapy, usually, patients are treated in both hospitals on their course of their disease. We included all patients who had a definitive histological diagnosis and had started treatment, be it surgical or chemo or radiations. Those patients who had no clearly documented treatment plan and date of onset of treatment and or diagnosis in their case notes were excluded from this study. Furthermore, patients who were discharged and were not traceable by phone call were excluded from this study.

Permission to carry out this study and ethical clearance were sought and obtained from the MUHAS institutional Review Board (IRB). The department of Surgery MUHAS endorsed the study and the Ethical committee of MNH cleared the study protocol.

The study involved all patients who had received care at MNH and ORCI from January 2015 to December 2017 with the diagnosis of oesophageal cancer. The recruitment process was such that all patients who had an established diagnosis of oesophageal cancer, by histology report from the central pathology laboratory of MNH or outside MNH and was accepted by the treatment team to start treatment. The initial time of treatment was taken as zero time of

survival. Included all the patients from this initial time of treatment until the end of December 20017, however their survival was evaluated beyond this period up to 2yrs. Thus, we had a chance to speak directly to very few patients who were still alive during the time of data collection.

The sample size was estimated using the proportion of previous study done by Gabel J. V et al at ORCI in 2016 (10), with the proportion (P) of oesophageal cancer in Tanzania at 9.2% and the confidence interval at 95%: the sample size (n) was equal to 128, that is 64 patients from MNH and other 64 patients from ORCI. A structured data collection tool was used to extract data. Information on year, month and date of death was obtained in patients' files if they died in a hospital setting, but for those who were still alive, information was obtained by calling the next of kin or the patients themselves. Information on the degree of dysphagia four weeks after treatment was also obtained in patients' files if they happened to stay in the ward for four weeks after treatment or by calling the next of kin of the patient. The estimation of degree of dysphagia was carried using subjective parameters which are used in the standardized scale that summates to grades which range from grade 0 to grade 6. These subjective parameters are easily obtainable by both one on one discussion or through phone calls. All information obtained collected in a structured data collection tool was coded and carried no patients' names to ensure confidentiality. These were entered and analysed in computer software of SPSS version no 20. The computer folder files are protected under a special password. Data was analysed using percentages, and significance of differences was deduced using X^2-square test. A p-value of 0.05 where appropriate was regarded as the cutoff point to detect any statistical significance.

Duration of recurrence

Duration for recurrence of symptoms was also obtained from patients' files if they happened to be readmitted. Those who had a recurrence that was not documented in the files; the determination was through calling the next of kin of the patient. Recurrence was determined by either reappearance of clinical symptoms or through investigational findings. Clinical symptoms ranged from dysphagia, regurgitation, retrosternal pain, difficulty in breathing, choking and change in voice, clinical signs such as a mass on the necks and investigational findings such as evidence of mediastinal metastasis by CT scan or chest X-ray and abdominal metastasis by ultrasound or CT scan.

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Results

The study involved 128 patients with a mean age of 55.9 years ranging from 20 to 91 years. Males were the majority (60.2%). The majority of patients had SCC at 92.2 %. All of the Adenocarcinoma cases were found in the distal part of the oesophagus. The Majority of patients (44.0%) took up to three months from initial symptoms to reach a tertiary/national Hospital.

Table 1: Baseline characteristics of study sample

	Number (%)
Age group	
20-39	20 (15.6%)
40-59	53 (41.4%)
60 and above	55 (43.0%)
Sex	
Male	77 (60.2%)
Female	51 (39.8%)
Duration of the symptoms at diagnosis	
Less than one month	2 (1.5%)
One to three months	55 (43.0%)
Four to six months	47 (36.7%)
Seven to nine months	10 (7.8%)
Ten to twelve months	11 (8.6%)
One year to two years	3 (2.3%)
Stage of the disease	
Stage I	0 (0.0%)
Stage II	12 (9.4%)
Stage III	58 (45.3%)
Stage IV	48 (37.5%)
Unknown	10 (7.8%)

Histological distribution according to tumor location	**SCC**	**AD**
Proximal third	36 (100%)	0(0%)
Middle third	53(100%)	0(0%)
Distal third	25(80.6%)	6(19.4)
Undocumented	4(50%)	4(50%)
Total	**118(92.2%)**	**10(7.8%)**

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The figure below shows the 2-year survival curve of patients. Survival rate (proportion of surviving) is steep in the 1st month then it decreases sharply in the first six months, maintaining an almost constant rate thereafter one year onwards. After 3 months almost half of the patients had died. The 2-year survival rate was 0.08=8%. Many patients died in the first month such that after the first month, the proportion of survivors had decreased to 59% (0.59). Life expectancy after initiation of treatment was 6.52 months.

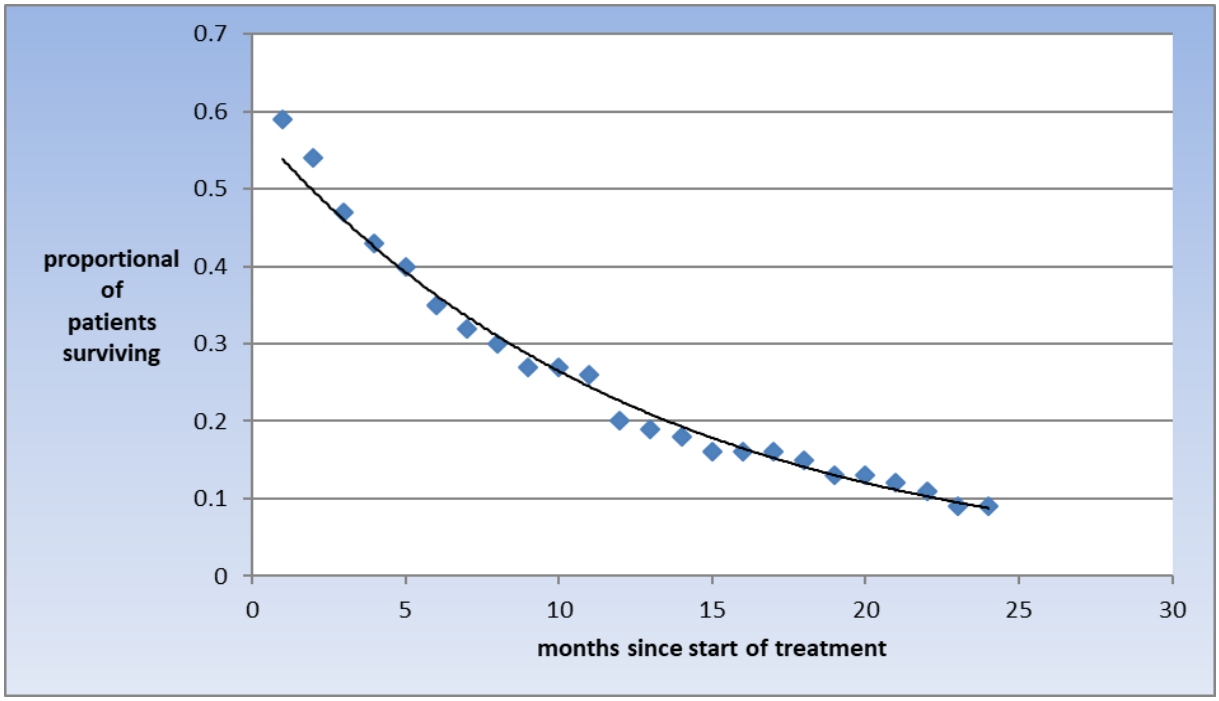

Figure 1. Two-year esophageal cancer survival curve

The level of dysphagia was taken from all patients within 4 weeks of completion of treatments (either surgery, chemoradiotherapy), irrespective of the time of death. 35(27.3%) of patients died during the course of treatment (before completion of a specific treatment offered) which was due to treatment complications, therefore their level of dysphagia was not recorded. All in all, dysphagia improved in all the recorded patients regardless of grade.

Table 3: Grade of dysphagia at four weeks of treatment

Grade of dysphagia	Before treatment	After treatment
No dysphagia	1 (0.8%)	4 (3.1%)
Grade I-II	4 (3.1%)	20 (15.7%)
Grade III-IV	123 (96.1%)	69 (54.1%)

From the table below, the mean duration for dysphagia recurrence was 3.6 months (SD 1.9 months, 95% CI, 2.4- 4.8), for distant metastasis the mean duration was 7.1 months (SD 6.7 months, 95% CI, 2.2- 12.0). Recurrence was documented in 28 patients. There was no adequate data to suggest the status of the rest of patients because some of them had died before the evaluation. The commonest site for new metastases was the supraclavicular area. The local recurrence was frequently noted in the 1st 4months by 61%. The distant metastases mostly were noted in the 1st six months since initial treatment.

Table 4: Recurrence of symptoms and metastases after treatment

Recurrence of the symptoms and metastasis	Number (%)
Yes	28 (21.9%)
Not documented	100 (78.1%)
Pattern of recurrence	
Local	21 (75%)
Distant	7(25%)
Site for new distant metastasis	
Supraclavicular	4 (57%)
Abdominal	2 (28%)
Bones	1 (15%)
Duration for local recurrence (in months)	
1-2	6 (28%)
3-4	7 (33%)
5-6	5 (23%)
7-8	3 (16%)
Duration for occurrence of new distant metastasis (in months)	
1- 6	3 (43%)
7- 12	1 (14%)
12 – 18	1 (14%)
19- 24	2 (29%)

Majority of the patients received chemoradiotherapy with a survival of 8(11.6%) out of 69 patients. The 2-year survival rate was relatively higher in surgery+adjuvant chemoradiotherapy group at 33.3% (1 patient), while that of radiotherapy and chemoradiotherapy were at 18.2% (2 patients) and 16.7% (2 patients) respectively. (Chi-square of 48.6 and p-value of 0.016). One patient who received chemotherapy alone survived for the entire period. Feeding gastrostomy and stents had the poorest survival chance.

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Table 5: Analysis of effect of treatment modalities to Survival chances

Type of definitive treatment	Survival (no. of patients)			
	At zero time	2months	12months	24months
Chemotherapy alone	1(100%)	1(100%)	1(100%)	1 (100%)
Radiotherapy alone	12 (100%)	12(100%)	10(83.33)	2 (16.7%)
Chemoradiation	69(100%)	30(43.48%)	19(27.54%)	8 (11.6%)
Surgery+adjuvant chemoradiotherapy	3(100%)	3(100%)	2(66.67%)	1 (33.3%)
Feeding gastrostomy and stents	43(100%)	6(13.95%)	0(0.00%)	0 (0.0%)
Total	**128**	**52**	**32**	**12(9.3%)**

Discussion

Among the total cases of 128 patients, the male to female ratio was 1.5:1, the majority of the patients were in the 5th, 6th, and 7th decades at 55.4% with the mean age of 55.9 years. This is consistent with the study done in Pakistan whereby the mean age was at 56 years (11).

Our study sheds some light regarding the age of affected patients. This disease has been regarded as the disease of the elderly citizens with poor survival chances. The pattern of the disease evidenced by a number of previous studies including our study indicates that the cancer dynamics involve the younger generation at their 40s and 30s. Nevertheless, from the pathogenesis point of view, it would be imperative to consider the fact that, it takes long time at least 5 years or so for one to have his oesophageal lumen occupied by the tumor by more than 50 percent. This is an important factor needed before any significant dysphagia develops. When we examine this fact and tie down our data, we also postulate that, this change in dynamics is an apparent biostatic finding, that might have occurred under the umbrella of improving diagnostic services in the country, such as access to endoscopic studies and interventions.

Our study involved patients who came to the National hospital 3 months on average from the onset of symptoms. This, to our opinion, is too long and underpins the kind of access to quality health care these patients get. It has been established in the literature that delayed medical treatment can lead to an advanced stage of the disease at the time of diagnosis (10). Our patients in this report were able to receive medical care at both MNH and ORCI

while the disease was stage III and IV disease at the time of diagnosis (83.1%). These two stages are considered locally and systemically advanced, respectively and carry a poor prognosis in terms of both quality of life and survival chance.The effect of the referral system to delayed medical care and its consequences to progressions of the disease was not particularly examined in this study. Nevertheless, the results of our study imply that delayed diagnosis led to poor overall 2- year survival rate of 8% with life expectancy of 6.52 months after initiation of treatment.

The 2-year survival rate was high in surgery and adjuvant chemoradiotherapy group at 33.3%, while that of radiotherapy alone and chemoradiotherapy were at 18.2% and 16.7%, respectively (P-value of 0.016). This is a group of patients who are usually found to have good clinical performance at the outset of pre-treatment evaluation and therefore deemed capable to withstand the surgical stress and chemoradiotherapy combined effect. Some other factors (27,29) unknown to this study may have played a role in better survival rate in that category, and therefore we hereby invite further scientific scrutiny in order to strengthen and improve their provisions. In other words, one would suggest that palliative treatment should be offered using these two modalities, because the others like radiotherapy alone have an inherent poor survival effect. An argument there arises, as these patients who end up with later treatment are usually those with poor clinical performance whose tolerance to combined chemoradiotherapy modality of treatment is poor, we therefore suggest that these patients should be captured early before they clinically deteriorate. This is also true for the study done by Merkow P et al, in 2012 in the United States which found that the median overall survival of patients treated by chemoradiotherapy and surgery in stage II and III adenocarcinoma of the esophagus was 23.4months while for chemoradiotherapy alone was 10.6 months, also chemoradiotherapy and surgery was associated with low risk of death compared to chemoradiotherapy alone(5).There is a strong need for general population awareness of the nature of the disease to be raised, plus the strong implication to the need to strengthen the health referral system of the country in order for the diagnosis to be made at the earliest possible stage. The survival rate in our study looks much lower compared to that in Iran in which the 2-year survival rate was 52.8% (12) and in a study done in Texas, the USA which was between 59% and 60% (13). The difference is due to the fact that the patients in these two studies were in the early stages of the disease at diagnosis. The results show that, majority of the patients died in the 1st month of initiation on any treatment modality except for surgery, where more than 40% of the study population had already died

by the end of the 1st month. This, coupled with the fact that, only a small fraction of these patients get to access stenting services prior to chemo or chemoradiotherapy, gives an impression of the significance of disease severity, stage, nutritional impairment, and overall clinicopathological performance status of such patients at the time of treatment induction (9,10). The performance outcome of the treatment modalities offered at ORCI and that offered at MNH is highlighted by the findings of improved dysphagia at the earliest 4th week of treatment. We see in this study, that those patients who had grade 3 to 6 dysphagia, had seen their dysphagia improving to either grade II, I or no dysphagia at all from 96% down to almost 50%. This seems to be an encouraging fact, but we noted also that, it is within this critical period of treatment that the mortality rate was observed to be the highest. Those who reported improvement survived this period for reasons unknown for now in this report. This highlights the importance of critically scrutinizing the indications for chemoradiotherapy and probably gives hard evidence to the actual performance of these treatment modalities of oesophageal cancer. That is to say, even if there is significant improvement in those who survive the 1st month of initiation of treatment, their symptomatic improvement only sustains an average duration of 3.6 months within a period span of 2.4 to 4.8 months. Additionally, these improvements may have happened at the expense of high mortality during this short period from initiation of treatment. These findings raise a number of questions such as this: why should these patients succumb to death at this high rate just after treatment induction. Is it true that these palliative treatments have a direct negative impact on these patients? what would be the outcome if these patients were not treated by any of these modalities. These questions may be answered probably by another study design.

We hypothesize that this observational outcome could be due to differences in disease stage between individuals, the differences in biological nature of tumor, nutritional support and status and probably they had already received the oesophageal stenting. Nevertheless, a significant number of these patients had already received a surgical feeding procedure in order to prepare them for the chemoradiotherapy and therefore had a good nutritional status adequate enough to withstand the stress associated with treatment induction. These facts fall short of the primary objective of this study and probably we need to give another/separate study to explore these important areas, namely the analysis of factors associated with poor survival in Oesophageal cancer patients during the treatment induction.

It is noted in our study, that local and systemic symptoms recurred after an average period of 3.6 and 7months respectively. The mean duration for dysphagia recurrence was 3.6 months

(SD 1.9 months, 95% CI, 2.4- 4.8), and for distant metastasis the mean duration was 7.1 months (SD 6.7 months, 95% CI, 2.2- 12.0).

Recurrence was another important secondary end point of our study. In this report, Recurrence means reappearance of symptoms, physical signs and/ positive diagnostic imaging or endoscopic report indicating reappearance of the disease after having evidence of clinical improvement. We found in our study that 28 out 128 (21.9%) patients had established recurrence. These recurrences were noted to develop within an average period of 3.6 months. The most significant finding among this group of patients is the time period of sustained improvement in dysphagia, despite being transient. The findings in table 3 also show that about 100 patients did not have a documented recurrence. It included all the patients who never improved including those who died before the evaluation. This result underscores the fact that, whatever the palliative treatment that was offered, these patients did not improve over the course of treatment and in fact they died sooner or later by the time of this studies evaluation. We cannot at this juncture recommend over the benefit or harm of these patients on treatment induction. Nevertheless, the extent of bias to reporting and documentation of these findings, may be overestimated, and hence to get these answers correctly, a prospective study should be designed (6).

Looking at the distant metastasis, supraclavicular area was seen to be the commonest site of distant metastasis with 5 patients (57.1%) followed by few cases of abdominal and bone. The Mean duration for distant metastasis was 7.1 months (ranging from 2.2months to 12.0 months). It is therefore correct to draw inference from the survival table that the most likely cause of a surge in mortality at 5th past 6th and 7th month was due to the disease progression including systemic spread. This inference has been well demonstrated in a number of other reports (9, 11, and 14) and that patients who suffer recurrences have the poorest survival rate than any other patients with oesophageal cancer (14).

Conclusion

The survival chance of patients receiving treatment at a National Hospital in the country is slim, with figures indicating survival rate of 8% at 2yrs. There is a significant loss of patients in the 1st month in the course of treatment. For those who survive the 1st month of treatment, their symptoms albeit short lived improve significantly. The median time of recurrence of dysphagia and other symptoms of oesophageal carcinoma after treatment is 3.7months. Overall, the disease's natural course is unaltered by the kind of treatments offered at a national and tertiary level.

Recommendations

Late diagnosis was the main factor for poor outcomes that renders patients to receive only palliative therapy. Hence, stronger emphasis should be made on early detection of the disease so as to increase the number of patients who would get definitive treatment of cancer (surgery, radiotherapy, or/and chemotherapy) and subsequently increase the overall survival rate and improvement of symptoms after treatment.

We recommend strongly that whatever is given as a form of palliative care must be equated against the high risks of morbidity and mortality that happens during the 1st month of initiation of treatment. This balance must be determined by performing another study analyzing the factors that interplay to determine the outcome of either harm or benefit to this group of patients.

More emphasis is hypothetically sought towards making sure that nutritional support and correction is instituted early in the initial phases of treatment before initiation of some kind of chemoradiotherapy. This is assumed that morbidity and hence mortality will decrease in the 1st month of treatment.

Competing interests

There are no competing interests to declare.

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Abbreviations

AC	Adenocarcinoma
CRT	Chemoradiotherapy
MNH	Muhimbili National Hospital
MUHAS	Muhimbili University of Health and Allied Science
ORCI	Ocean Road Cancer Institute
SCC	Squamous Cell Carcinoma
WHO	World Health Organization

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Appendix

I. Statistical analysis:

The gathered information was entered into the SPSS computer program**.** The obtained information was summarized by tables and charts

Life table for 2-year survival rate was obtained from the formula for calculation of life tables such as

i) Treatment interval was given in months from the start of treatments up to 24months (two years)
ii) Number alive at the beginning of interval was calculated from subtracting the number died from the previous intervals with total number of patients at the start of previous interval
iii) Death during interval, these were the total number of patients who died during the interval
iv) Number lost to follow up, we excluded this number since it was a retrospective study
v) Number of persons at risk=((ii)- iv/2)
vi) Number of dying during interval = (iii÷ v)
vii) Chance of surviving interval = 1- (vi)
viii) Cumulative chance of survival from start of treatment = previous interval× vii above

II. Survival curve was obtained by:

y axis- proportional of patients surviving (vii-above)

x axis- months since start of treatments (i-above)

III. Life expectancy was obtained from:

(Multiplication of length of interval by cumulative chance of surviving) + ½

i.e ½ + ∑ (number of months' interval times cumulative chance of surviving)

i.e. ½ + (i-above × viii-above)