Experience of Upper Egypt in Bladder preservation by using concurrent chemoradiotherapy

INTRODUCTION:

Radical cystectomy has been considered the treatment of choice for non metastatic muscle invasive bladder cancer. This approach that results in 90% local control at 5 years, and only 40% to 60% 5–year overall survival [1]..

In addition, there is a high incidence of life altering morbidity after radical cystectomy, such as the need for urinary diversion. As a result, alternative, bladder sparing treatment approaches have been explored. Trimodalitybladder preserving therapy, with combined transurethral resection, radiation, and chemotherapy, provides survival comparable with radical cystectomy. Five year survival with bladder preservation was 38% to 45% and 80% of the long term survivors maintained a functional bladder , with no apparent cost in terms of survival [2].

The majority of clinical trials in the past decade have used single agent 5–fluorouracil or Cisplatin for radiosensitization. In an attempt to improve safety and to increase efficacy , newer studies of multimodality therapy are including chemotherapeutic agents that have recently shown excellent activity in metastatic uroepithelial cancers , such as gemcitabine . Many phase II trials demonstrated that gemcitabine combined with cisplatin was well tolerated active regimen [3].

Patients and methods:

The first study was performed in the clinical oncology department, faculty of medicine, Sohag University between the period from September 2002 to April 2005.
30 patients with operable muscle invasive transitional cell carcinoma of bladder were included in this study and underwent transurethral resection followed by radiochemotherapy for selective bladder preservation.

Eligibility Criteria:

Disease characteristics:

Primary transitional cell carcinoma of the urinary bladder.TNM: (T2- T4a, Nx or No, Mo).Resectabledisease.Prostatic urethral involvement with transitional cell carcinoma was allowed, if it was completely resected and no stromal invasion. No distant metastases.

Patients characteristics

Age, 18-75 years.Performance status: 0-2 (from ECOG = Eastern Cooperative Oncology Group).

Laboratory studies:

Haemogram:haemoglobin was equal or more than 10 g/dl & WBC was equal or more than 3000 mm3 (neutrophil count equal or more than 1000/ mm3 & platelets count was equal or more than 100,000/mm3.

Hepatic: bilirubin was not more than 1.5 mg/dl & liver enzymes were within normal values.

Renal: creatinine was not more than 1.5 mg/dl.

No prior systemic chemotherapy or pelvic radiotherapy was given.

Treatment Plan:

Phase Iof radiochemotherapy treatment (weeks 1- 3)

Concomitant radio-chemotherapy was delivered within 3 to 4 weeks after transurethral resection.

Radiotherapy was given by Linear accelerator (6 MV), twice daily fractions of external beam irradiation was given as following, 1.6 GY was given to the pelvis field in the first fraction followed by an interfraction period of at least 4-6 hours, then, 1.5 GY was given to the bladder field in the second fraction, this treatment was given in days 1- 5 & 8- 12 & 15, 16 17. Chemotherapy

Chemotherapy was given combined with radiotherapy as following:

5- fluorouracil / (400 mg/m2) was administered as a 24- hour's infusion on days (1, 2, 3 and 15, 16, 17). Cisplatin / (15 mg/m2) was administered as a 60- minutes infusion on days (1, 2, 3 -- 8, 9, 10 -- 15, 16, 17).

The second study was performed during period from December 2004, to April 2006, 30 patients at Urology and Clinical Oncology departments, Assuit University Hospital were enrolled in this trial.

Eligibility Criteria:

Patients with histopathologically proved invasive bladder cancer,(T2 – T3b, No – Mo).Maximum resection of bladder tumor by transurethral resection, followed by second look cystoscopy for resection of any residual tumorat tumor bed after two

weeks, or by partial cystectomy.Karnofsky scale ≥ 70 %.Adequate hematological, hepatic and renal functions.Adequate bladder capacity ≥ 350 c.c. which was evaluated under anesthesia.

Exclusion criteria:

Locally advanced tumor (T4a, T4b), Positive lymph nodes, Distant metastasis.Patients received BCG or intravesical chemotherapy.

Treatment plan:

After complete resection of bladder tumor, patients received combined chemo-radiotherapy 60 Gy of fractionated radiotherapy (200 cGy per setting) over 6 weeks with Cisplatin 75 mg/ m2 q. 3 ws and Gemcitabine 300 mg / m2 D 1, 8 and 15 q. 3 ws for 2 cycles.

Results:

In Sohag study, 30 patients with operable transitional cell carcinoma of the bladder underwent maximum transurethral resection followed by radio-chemotherapy as an initial treatment.

Patients' characteristics table (1)

As shown in table (1): the age of patients in first study ranged from 35-72ys withMedian 56 years, 24 patients were male (80%) and 6 patients were female (20%). Performance status was represented as following, 23 patients (76.6%) were scale (1) and seven patients (23.3%) were scale (2).

All patients underwent transurethral resection, complete TUR in 8 patients and incomplete TUR in 22 patients (26.6%, 73.3% respectively) and 6 patients presented with obstructive uropathy (20%)

The T stages of the disease were distributed as following, 2 patients were diagnosed in stage T2a (6.6%), 9 patients in stage T2b (30%), 11 patients in stage T3a (36.6%), 7 patients in stage T3b (23.3 %) and one patient in stage T4a (3.3%).
18 patients (60%) were grade II and 12 patients (40%) were GIII and 13 patients (43.3%) their pathology wasassociated with bilharziasis.

Patients' characteristics of the second study (Assiut study), thirty patients (21 men and 9 women) with a mean of 57.3 ± 12.75 years (range 35-80 years) and a median 58.5 years with Karnofsky performance status ranged between 70-90% were

enrolled in this study. Forty percent of patients were non smoker .Their main complaint was heamaturea (100%) then triad of heamaturea, burning and necroturea (40 %).

As regard disease characteristics, pathological diagnosis of T2a was 7 %, T2b was 83 % and T3 was 10 %. Sixty percent of patients had positive history of Bilharziasis and 63.3 % of patients were transitional bladder carcinoma, 36.7 % were high grade and 33.3 % were located at anterior bladder wall

Response:

Initial response after phase Iand final response after phase II of treatment and of treatment :Table (2):

In Sohag study, after phase I of treatment the total response was 73.3% [13 patients (43.3%) had complete response, nine patients (30%) had partial response], seven patients (23.3%) had stationary response and one patient (3.3%) had disease progression. Patients who had complete and partial response (22 patients) received second phase of treatment and eight patients (26.6%) underwent salvage cystectomy.

After end of treatment, 15 patients (50%) had complete response and we followed them up, seven patients (23.3%) had partial response, seven patients (23.3%) had stationary response and one patient (3.3%) had a disease progression. Those patients underwent salvage cystectomy except one patient who refused it and received other treatment.

The completeness of transurethral resection (p- value: 0.012), and early tumor stage (p- value: 0.021) revealed the significant impact on the response.

In Assiut study,after conservative surgery 27 out of 30 patients were disease free at the time of the cystoscopic reevaluation 4-6 weeks after the end of treatment and were confirmed by the biopsies taken from the site of the primary tumor, three patients were stationary course, they were refused and they were treated with palliative chemotherapy.

Radio-chemotherapy related toxicity table (3) ***and*** table (4):

The above table shows, no life threatening acute toxicity in Sohag study noticed due to combined radio-chemotherapy. It can be noticed that, grade I anemia occurred in 3 patients (10%), GII occurred in 5 patients (16.6%), and those patients treated by Iron, no patients received blood transfusion. Grade I Leucopenia occurred in 6 patients (20%), GII occurred in 2 patients (6.6%), no need for supportive treatment and no interruption of the treatment occurred, and grade III leucopenia occurred in one patient (3.3%) after ending the first phase of treatment, prophylactic antibiotic was given till recovery. Grade I Thrombocytopenia occurred in one patient (3.3%) and GII occurred in one patient (3.3%).

Grade I&II gastrointestinal toxicities were noticed in many patients received radio-chemotherapy, no GIII, or IV toxicity was detected.

Grade III bladder toxicity was noticed in three patients, and the rest of patients had GI, II bladder toxicity, those patients were managed by symptomatic treatment. 10 patients experienced increase creatinine level (8 patients were GI, and 2 patients were GII), and those patients improved by I.V hydration. Seven patients had grade I radiation dermatitis.

On the other hand,inAssiut study the treatment was subjectively well tolerated, although anemia grade 3 was observed in one patient and grade 3 frequency occurred in 5 (16.5%)patients, dysurea in 2 (6.6%) patients and bladder capacity was reduced to less than 250 c.c. in 3 patients

Recurrence free survival

The follow up period ranged from 12 to 30 months with median 17 months, after end of treatment 15 patients were free of disease with bladder preservation and 15 patients did not have CR, 14 patients

underwent salvage cystectomy, (one patient refused cystectomy). During the period of follow up the group of preserved bladder, had four patients showed disease recurrence and the other group of salvage cystectomy had two patients showed disease recurrence. The actuarial disease free survival curve (Fig. 1)for both groups shows that, the disease free survival at the end of follow up (30 months) was 70% for the preserved bladder group and 75% for the salvage cystectomy group (P- 0.74).

Figure (1):- Recurrence free survival for complete responders (bladder Preservation) and non complete responders (with salvagecystectomy).

From the actuarial recurrence free survival curve for the whole group of patients (Fig.2), we noticed that the recurrence free survival at the median follow up (17 months) was 84% and at the end of follow up (30 months) was 70%.

Figure (2):- Recurrence free survival for the whole group.

Over all survival

Overall survival for both groups of patients (preserved bladder patients and patients with salvage cystectomy) represented as an actuarial curve (Fig.3). Overall survival for the preserved bladder patients at the end of follow up (30 months) was 92% and for the salvage cystectomy patients was 84%, (P-0.63).

Figure (3):-Overall survival for complete and non complete responders

The overall survival for the whole group of patients (preserved bladder and salvage cystectomy patients) at the median follow up was 95%, and

Figure (4):-Overall survival cure for the whole group

In the second study (Assiut)

Survival:

After conservative surgery 27 out of 30 patients were disease free at the time of the cystoscopic reevaluation 4-6 weeks after the end of treatment and were **Whole group** by the biopsies taken from the site of the primary tumor (One patient died after end of treatment due to other cause rather than disease progression and 2 patients were stationary course, they were inoperable (fixed) and they were treated with palliative chemotherapy.

Out of 27 patients 6 developed an infiltrating bladder relapse and one developed distant metastases (lung) during the 18 months follow up (Delayed cystectomies done to 3 patients and the others refuse to do cystectomy) . Disease free survival (D.F.S.) was 66.67% with mean 14.7 and median 18 months. Overall survival (O.A.S.) was 76.67% with mean 15.93 and median 18 months (Table 8&figures 5 and 6).

Three significant prognostic factors were detected for overall survival (O.A.S.) ,performance status with P.value= 0.032, tumor size with P.value=0.000 and residual of tumor with P. value=0.000 .

Two significant prognostic factors were detected for disease free survival (D.F.S.), tumor size with P.value=0.017 and residual of tumor with P.value=0.033.

Table (6): Distribution of Disease Free Survival (DFS) and Over All Survival (OAS) of all patients in the follow up period (18 months):

Fig(5):Curve for disease free survival (D.F.S.) for all patients.

Fig.(6):Curve for overall survival (O.A.S.) for all patients

Discussion:

We will introduce our experience in bladder preservation in Assiut and Sohag using different protocols. In Sohag studythe age of patients ranged from 35-72ys with Median 56 years, 24 patients were male (80%) and 6 patients were female (20%). Performance status was represented as following, 23 patients (76.6%) were scale (1) and seven patients (23.3%) were scale (2).

In Assiut study the mean of age was 57.30 years, median 58.5 and range (35-80) years with peak incidence in 7th decade (9 cases) then in 6th decade 7 cases (23.33%) and that was comparable with series of Zaghloul et al, 2002 in which the mean of age was (56.24) and the peak of incidence was in 6th and 7th decades [4].. It was also comparable with western studies in which the incidence increases with age and peaks in the sixth and seventh decades of life [5].

Comparison between criteria of patients in present studies and other series is presented in table (5).

Table (5): Comparison between patients number, clinical stages, grades, and tumor type, in our studies and other series :

In Assiut study, 90% of patients were disease free at the time of cystoscopic reevaluation and this is in agreement with the results of Danesi, et al. 2004 in which complete response 90. 3% and they treated their patients by transurethral resection, protracted intravenous infusion chemotherapy (cisplatin and 5 F.U.), and hyper fractionated radiotherapy [6]. The response in this study is also comparable to that reported by Caffoet al., 2003 who reported a response rate of 100% and they treated their patients in phase I study of gemcitabine and radiotherapy plus cisplatin after transurethral resection as conservative treatment for infiltrating bladder Cancer [7]

On the other hand response was higher than reported by Ali et al.,2006 (SOHAG study) , in which they used (5-FU & cisplatin), concomitant with twice daily fractionated radiotherapy (accelerated hyperfractionation),) the total responders were 73.3% of patients (complete response was in 43.3% and partial response was in 30%)[8]. Rodel et al., 2002[9], using concurrent radiotherapy and 5-FU & cisplatin, complete response rate was 72%, Soliman, 2004,who reported total responders 76% (complete response was in 60% and partial response was in 16%) and they used also concurrent radiotherapy and 5-FU & cisplatin [10], and lastly higher than results achieved by Sakr, 2003, who reported 37% complete response rate, they used sequential chemotherapy (3 cycles Gemcitabine and Cisplatin) and radiotherapy[11].

Of concern is that within 18 months of follow up in Assiut study, 7 of 27 (74%) complete responding patients have had local recurrence and 66.7% of all cases. This is better than had been reported by Danesi D.T., et al., 2004 where local recurrence was 53.5%. The difference may be due to large number of patients in their study 72 patients and long follow up period 30 months [6]. Comparable result reported by Ali et al.,2006 (Sohag study) , who found that recurrence free survival for the preserved bladder patients at the median follow up (17 months) was 70%, and 75% for the group of salvage cystectomy. At the end of follow up (30 months) recurrence free survival for whole group of patients was 70% [8]. Higher results reported by Rodel, et al, 2002, who found disease free survival (at 18 months) of follow up was 80% and also by Soliman et al.,2004, who reported disease free survival (at 18 months) of follow up was 88.5%. It may be due to different histopathological subtypes in our study [10].

The overall Survival in Assiut study was 76.7%, and this is different from that reported by Kaufman et al., 2000 who reported an actuarial overall survival at three years 83%, the difference may be due to the use of induction treatment by

chemoradiation and patients with complete response received consolidation therapy with the same drugs and combined with twice daily radiation therapy for a total of 20 Gy[12]. And it is also lower than reported by Ali et al., 2006 (Sohag study) , who detect overall survival for preservation group and primary cystectomy group at median follow up 17 months were 95% and 92%, respectively, and at the end of follow up 30 months were 84%, and 78% respectively[8]. But it was comparable with results reported by Rodel, et al, 2002, who found overall survival (at 18 months) of follow up was 74% [9].

Three significant prognostic factors were detected for overall survival (O.A.S.) ,performance status , tumor size and residual of tumor and two significant prognostic factors were detected for disease free survival (D.F.S.), tumor size and residual of tumor in Assiut study and that was comparable to Rodel, et al, 2002 who reported that disease stage, grade and the extent of TUR were the significant factors affecting the response[9]. And it is similar with that reported by Ali et al.,2006 (Sohag study) who found the completeness of TUR and early stage of the tumor had the strongest impact on the response[8], In Soliman et al., 2004, the ureteric obstructive uropathy and bilharziasis were found to be significant prognostic factors[10].

The treatment was subjectively well tolerated, although anemia Grade 3 was observed in one patient and Grade 3 cystitis occurred in 5 patients and bladder capacity was reduced to less than 250 c.c. in 3 patients and that was similar with that reported by Caffoo et al., 2003 as grade 3 hematological toxicity was in l patient[7]. Also it was comparable to Ali et al., 2006 (Sohag study) in which grade 3 leucopenia in one patient and 2 patients (6.6%) had GIII dysuria, and one patients (3.3%) had GIII frequency [8]. More hematological toxicity reported by Kaufman, et al, 2000, who found 21% of patients developed GIII- IV hematological toxicity, and Rodel, et al, 2002, reported 23% of cases had GIII leucopenia, and 4% had GIII anemia[11], [9].

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Figure 1

Figure (1):- Recurrence free survival for complete responders (bladder Preservation) and non complete responders (with salvage cystectomy).

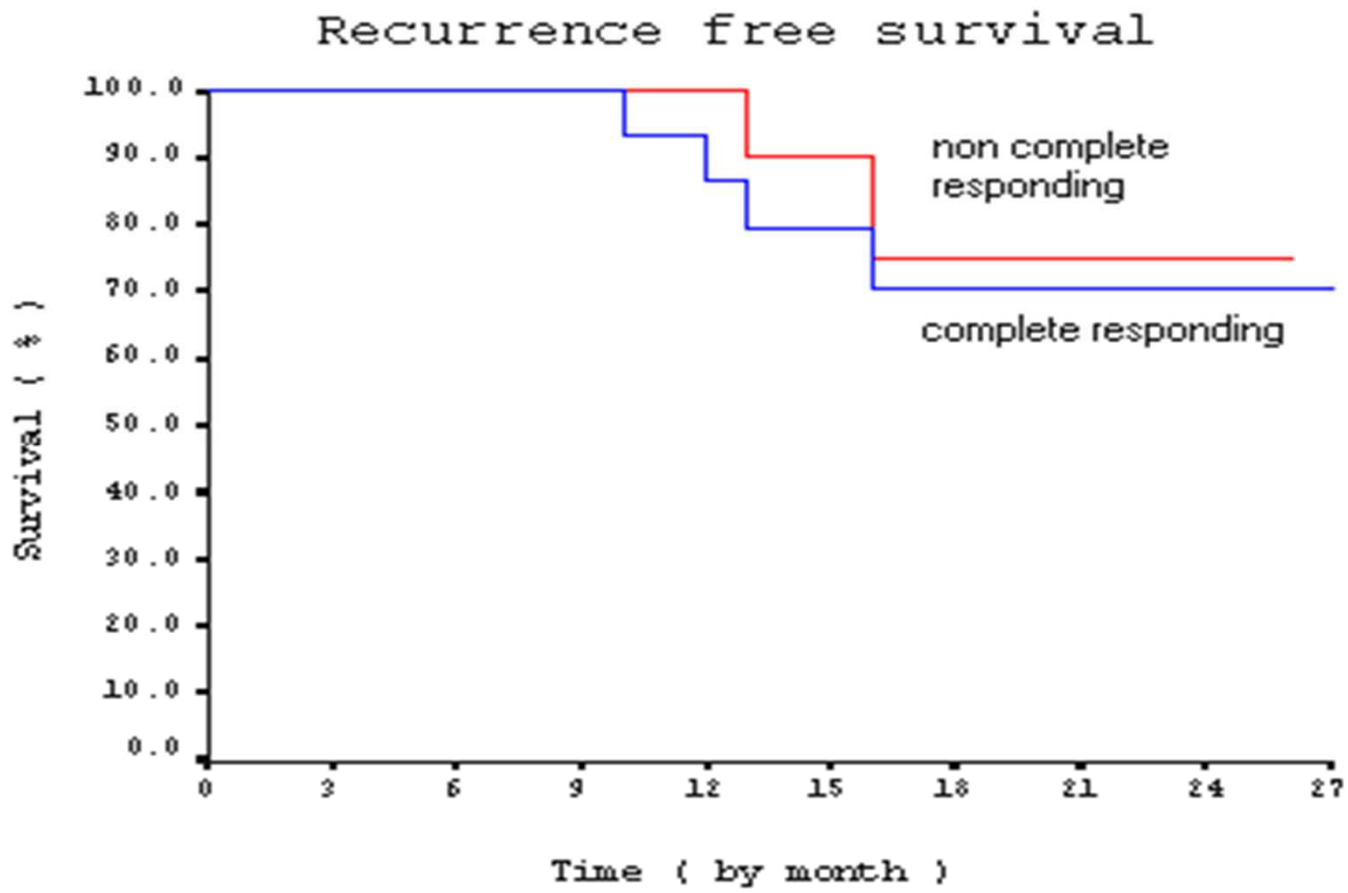


Figure 2

Figure (2):- Recurrence free survival for the whole group.

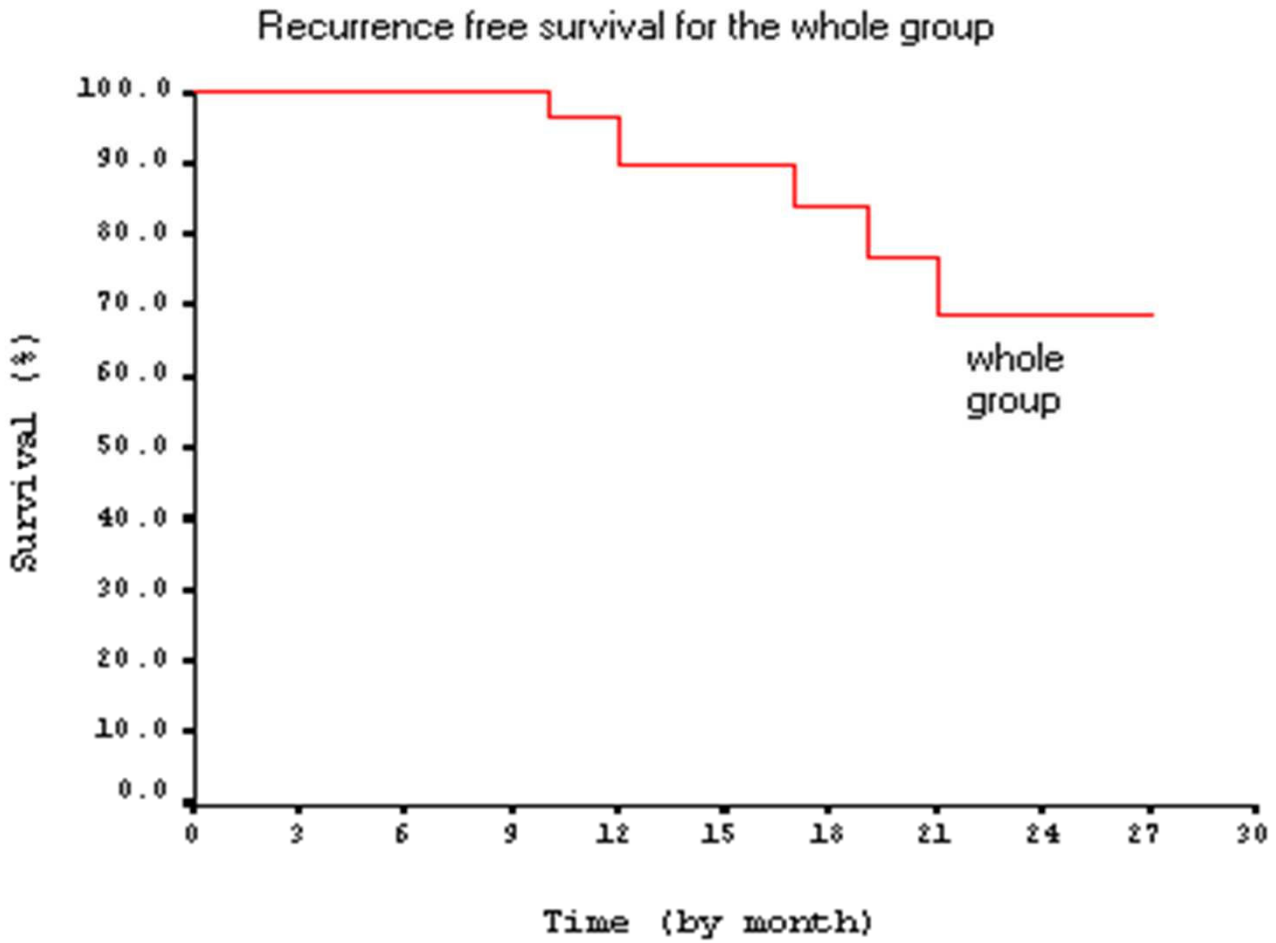


Figure 3

Figure (3):-Overall survival for complete and non complete responders

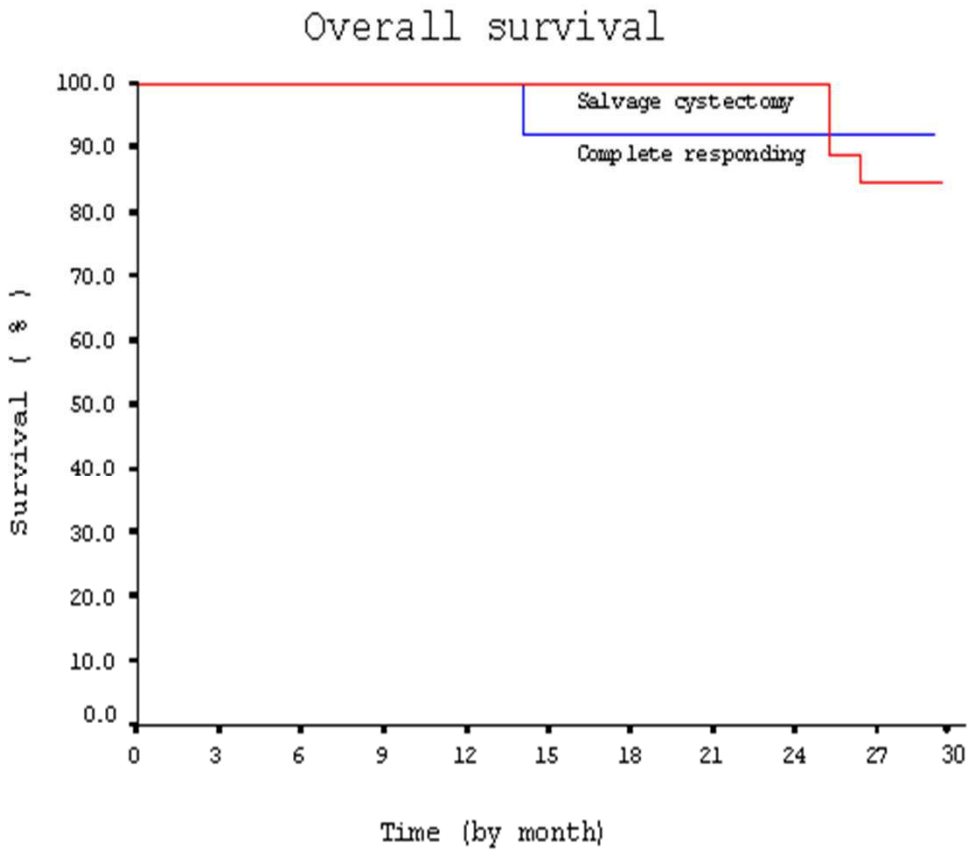


Figure 4

Figure (4):-Overall survival cure for the whole group

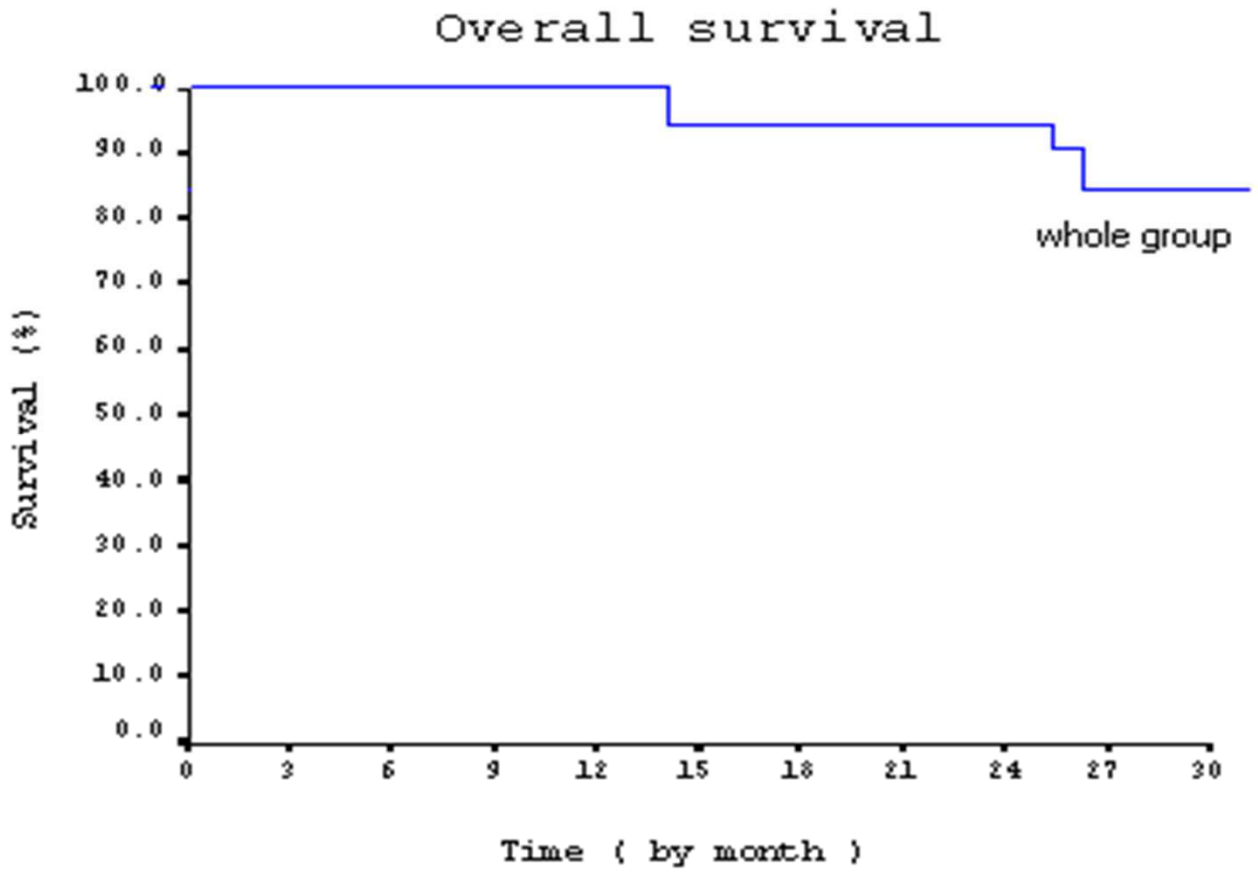


Figure 5

Fig(5):Curve for disease free survival (D.F.S.) for all patients.

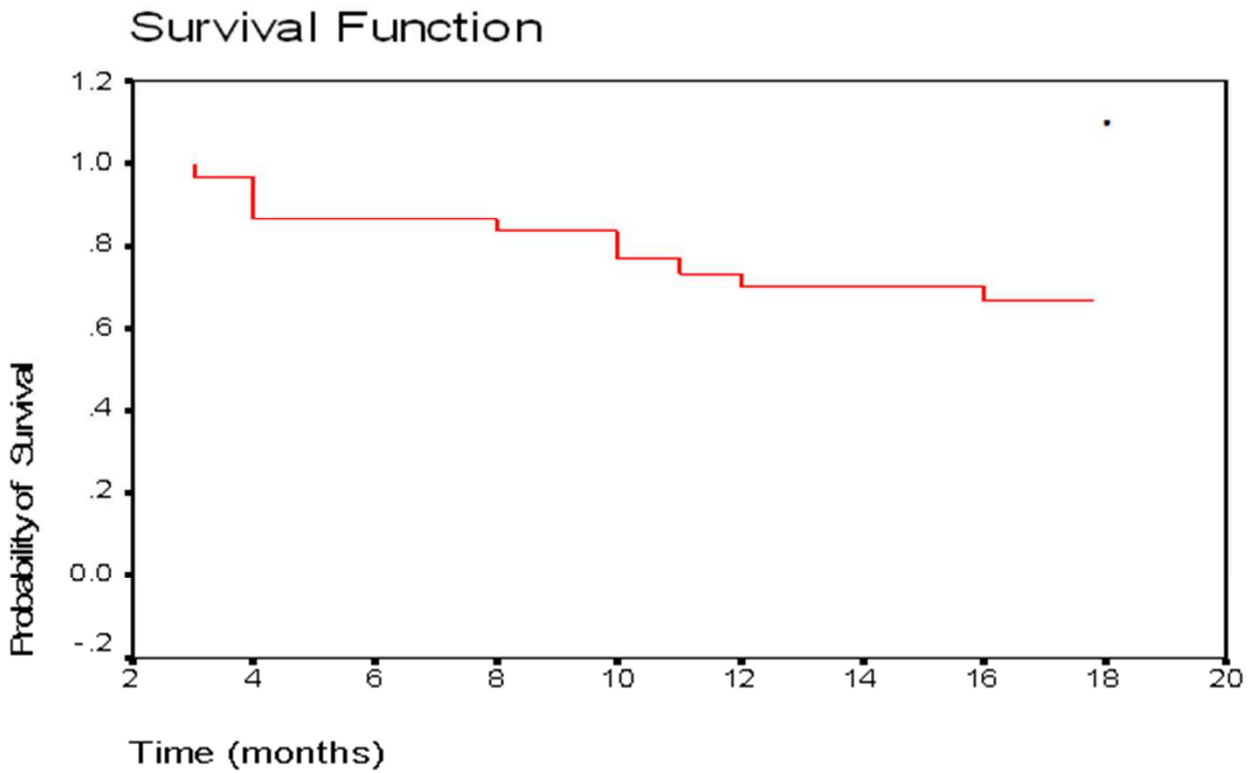
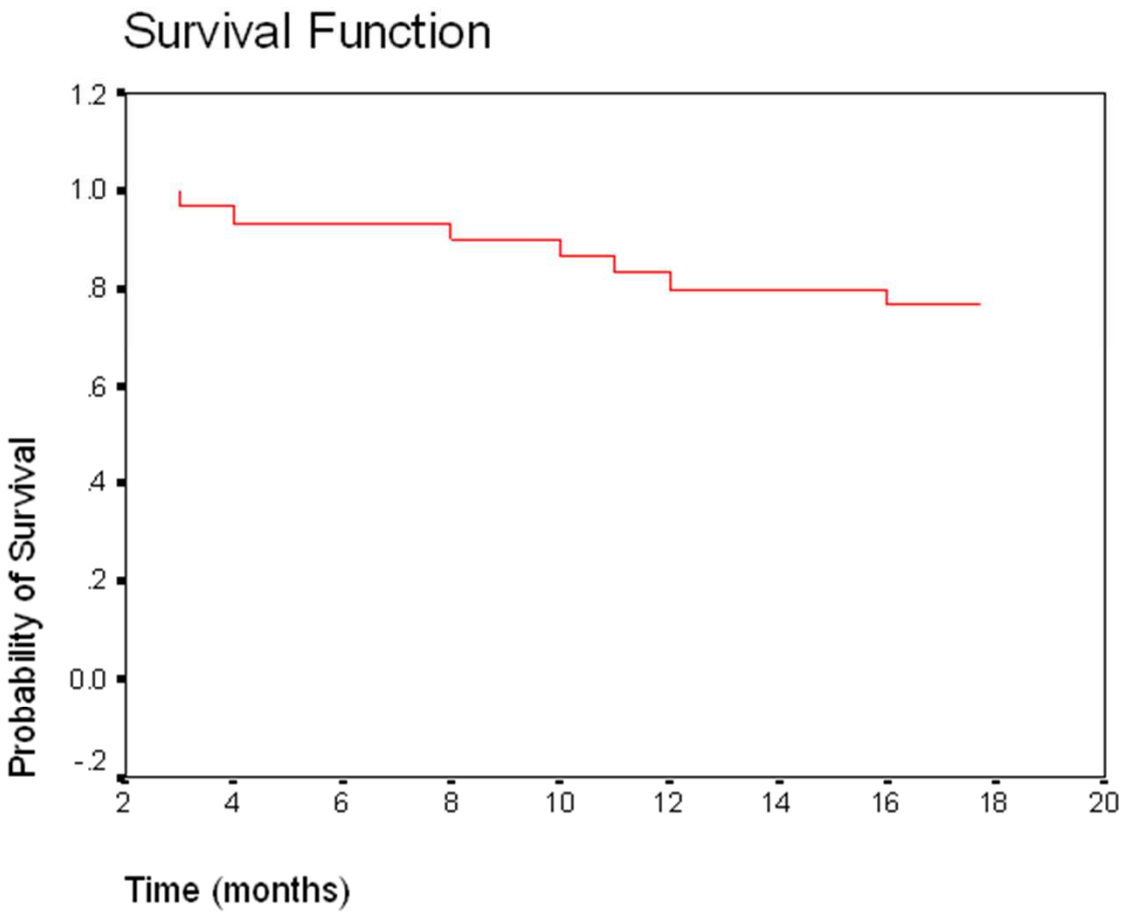


Figure 6

Fig.(6):Curve for overall survival (O.A.S.) for all patients



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