Radical Esophagectomy After Neoadjuvant Chemoradiation: Single Institutional Experience from Tertiary Cancer Centre in India

Ashish Goel, Swati H. Shah, Veda Padma Priya Selvakumar, S. Kahkasha, Shubha Garg, Anjali K. Pahuja, Kumardeep Dutta, et al.

Indian Journal of Surgical Oncology

ISSN 0975-7651

Indian J Surg Oncol
DOI 10.1007/s13193-015-0402-3

Springer

Indian J Surg Oncol
DOI 10.1007/s13193-015-0402-3

ORIGINAL ARTICLE

Radical Esophagectomy After Neoadjuvant Chemoradiation: Single Institutional Experience from Tertiary Cancer Centre in India

Ashish Goel[1] · Swati H. Shah[1] · Veda Padma Priya Selvakumar[1] · S. Kahkasha[1] · Shubha Garg[1] · Anjali K. Pahuja[1] · Kumardeep Dutta[1] · Ullas Batra[1] · S. K. Sharma[1] · D. C. Doval[1] · Kapil Kumar[1]

Received: 26 December 2014 / Accepted: 18 March 2015

Abstract Although preoperative chemoradiation has shown to improve surgical outcomes in both loco-regional control and long term survival; it has still not become the standard of care in many centers. There is reluctance in accepting preoperative chemoradiation primarily due to fear of increased perioperative morbidity/mortality or non-availability of infrastructure and expertise. We present a retrospective analysis of our results of radical esophagectomy after neoadjuvant chemoradiation. All patients who underwent Radical Esophagectomy from January 2009 to December 2013 by a single surgical team at our institute were included in the series (n=118). Patients undergoing surgery after chemo-radiation (group A= 66) were compared with those under going upfront surgery (group B=52) in terms of patient variables (age, sex, comorbidities, tumor location, staging, histology) and postoperative surgical outcomes and complications using Chi square test. Overall and disease free survival was analyzed using Kaplan Meir curve. There was no difference in duration of surgery, postoperative stay and overall morbidity and mortality in both groups. Although group A patients had more of advanced cases clinically, but histopathology showed complete pathological response (pCR) in nearly 40 % patients and negative nodes (pN0) in 62.5 % patients. OS and DFS showed a trend towards better survival with preoperative chemoradiation. We conclude that radical esophagectomy after preoperative chemoradiation is feasible and safe in developing countries. Moreover pathological complete response correlates well with improved survival. Randomized control trials may be required to further substantiate the results.

Keywords Chemoradiation · Radical esophagectomy · Esophago-gastric anastomosis

Background

Esophageal cancer is the eighth most common cancer worldwide, with nearly 145,000 new cases diagnosed in 2012. Overall the incidence remains highest in Eastern Asia and lowest in Western Africa [1]. There has been a rapid increase in incidence of esophageal cancer in India and a wide variation across major regions (Males 6.3-10.3/100000; Females 2.6-7/100000) [2].

✉ Ashish Goel
dr_ashishgoel@yahoo.com; dr.goelashish@gmail.com

Swati H. Shah
drswati2002@gmail.com

Veda Padma Priya Selvakumar
privedsri@gmail.com

S. Kahkasha
kahkashasiddiqui@gmail.com

Shubha Garg
shubhambbs99@gmail.com

Anjali K. Pahuja
anjali_kakria@yahoo.com

Kumardeep Dutta
kumardeep.d@gmail.com

Ullas Batra
ullasbatra@gmail.com

S. K. Sharma
drsksharma07@gmail.com

D. C. Doval
dcdoval@gmail.com

Kapil Kumar
kdrkapil@yahoo.com

[1] Rajiv Gandhi Cancer Institute and Research Centre, Sector 5, Rohini, New Delhi 110085, India

Published online: 16 April 2015

Total new cases detected in India in 2012 were 27,152 in men (7th most common cancer) and 14,622 in women (6th most common cancer) [1]. Together with prostate, liver and lung cancer; it is the leading cause of cancer related mortality across the globe, causing more than 400,000 deaths per year [3, 4].

The management of esophageal cancer is still evolving. The role of preoperative chemoradiation and chemotherapy has been debated for several years. Most of the earlier randomized trials failed to show any survival benefit with either approach. Most of these studies had concerns of poor study design, small sample size and poor overall survival in surgery alone group [5–7]. However the randomized controlled trial by Walsh et al. did show improvement in median survival with multimodality treatment [8, 9]. The most recent meta-analysis did suggest overall survival benefit with preoperative chemoradiation compared to preoperative chemotherapy across all patient groups (squamous and adenocarcinoma [10].

Kelsen et al. in a randomized trial on preoperative chemotherapy vs upfront surgery showed an R1 resection rate of 25 % in patients with primary surgery and 5 year overall survival less than 40 % [11]. The most recent randomized trial on the role of neoadjuvant chemoradiation and surgery did show a statistically significant improvement in disease free survival (DFS) and overall survival (OS) with preoperative concurrent chemoradiation followed by surgery compared to surgery alone [12]. Inspite of Level I evidence; preoperative chemoradiation followed by radical esophagectomy is still not the favored treatment modality in most centers in India and other developing countries. Overall there has been a general reluctance to accept the protocol of preoperative chemoradiation for esophageal cancer due to fear of increased perioperative morbidity / mortality and non-availability of infrastructure facilities; i.e. medical, radiation and surgical oncology under one roof.

Aims and Objective

To carry out a retrospective analysis of induction therapy followed by surgery for carcinoma esophagus in terms of early and delayed postoperative outcome and survival analysis.

Methods

We carried out a retrospective comparative study of patients undergoing radical esophagectomy after neoadjuvant therapy (preoperative chemotherapy or preoperative concurrent chemoradiation) versus patients undergoing upfront surgery at Rajiv Gandhi Cancer Institute and Research Center, New Delhi, India.

Clinical data was collected using HIS Vista ®. A total of 118 patients who underwent Radical Esophagectomy from January 2009 to December 2013 were included in the study. All surgeries were performed by a single surgical team.

Treatment protocol included initial assessment by UGI Endoscopy & Biopsy for tissue diagnosis and disease staging by CECT Chest and Abdomen or Whole Body FDG^{18} PET CT. Most patients with clinical stage T2/N2 or above underwent preoperative therapy (Group A; $n=66$) concurrent chemoradiation or preoperative chemotherapy. Patients found suitable for upfront surgery underwent preoperative workup with CBC, KFT, LFT, Viral Markers, Blood group and Type screening, 2D Echo and PFT followed by radical esophagectomy (Group B; $n=52$) after pre-anaesthetic assessment and optimization. Preoperative concurrent CTRT was done by IMRT /3D CRT to a total dose of 50.4 Gray / 28 # with weekly CDDP (Cisplatinum). All patient tolerated the treatment well with Grade 3 or 4 toxicity in 6 % patients only. Disease response assessment was done at six weeks of completion of therapy with Whole body FDG^{18} PET CT followed by Radical Esophagectomy there after. Seven patients received preoperative chemotherapy only for locally advanced GE Junction adenocarcinoma with three weekly cisplatinium based chemotherapy.

Different patient variables analyzed included patient age, sex, presence or absence of comorbidities; various tumor characteristics including tumor location, histology and clinico-radiological stage. Treatment variables studied included type of surgery (Transhiatal/ Ivor Lewis/ Mckeown) and surgical approach (conventional open/ thoracoscopic esophagectomy).

Data was analyzed to assess feasibility of surgery after neoadjuvant therapy, to include total operative time, ICU/ Hospital stay, early and delayed surgical complications and survival (DFS and OS). Besides routine histopathological parameters, overall pathologic response and tumor margin status was studied with reference to preoperative therapy.

Statistical analysis was carried out using SPSS Version 22 (IBM). Outcomes were compared using Chi square test, p value of <0.005 was considered statistically significant. Disease free survival and overall survival was calculated using Kaplan Meir Curve.

Results

From January 2009 to December 2013, total of 118 patients underwent radical esophagectomy by a single surgical oncology team. Out of 118 surgeries performed, 66 underwent surgery after induction therapy (59 patients with preoperative concurrent chemoradiation and 7 patients with preoperative chemotherapy) while 52 patients underwent upfront surgery.

Patient Variables

Comparison of patient characteristics in group A and group B did not reveal any statistically significant difference in patient age, sex, and histologic subtype (Table 1). Nearly one fourth

Table 1 Comparison of patient variables in group A and B

		Group A	Group B	*P* value
AGE	>50 years	39(59.1 %)	42(80.8 %)	0.006
SEX	% of males	40(60.6 %)	38(73.1 %)	0.110
HISTOLOGY	SCC/ADC	57/9	39/13	0.091
TUMOR LOCATION	Mid/lower/GEJ	45/17/4	20/21/11	0.003
SURGERY	Ivor Lewis	4	8	
	Transhiatal	3	6	
	Mckeown	59(89.3 %)	38(73.0)	0.071
SURGICAL APPROACH	Open	54(81.8 %)	45(86.5 %)	
	MIE	12(18.2 %)	7(13.5 %)	0.061
CLINICAL STAGE	T1	0	1	
	T2	2	51	
	T3	56	0	
	T4	8	0	
	N0	39(59.1 %)	35(67.3 %)	
	N+	27(40.9 %)	17(32.7 %)	

of patients in group 2 were adenocarcinoma compared to 13.6 % in group A; and most patients were mid third esophageal cancers (45/66). On the other hand most patients in group B were lower third esophageal and GE Junction tumors (33/52). In both groups the most commonly performed surgery was Mckeown' Esophagectomy with two-field lymphadenectomy (89.3 % in group A and 73.0 % in group B); while others underwent either transhiatal or Ivor Lewis esophagectomy. Clinico-radiological stage grouping suggested more of locally advanced tumors (cT3/4) in group A (64/66). All patients in group B were either clinical stage T1or 2 (Table 1).

Surgical Outcomes

The mean operative time in group A and group B was 343 min and 335 min respectively, and was not statistically different (p=0.157). Mean duration of ICU stay in group A and B was 6.35 vs. 6.47 days respectively (p=0.314). Mean duration of total hospital stay was comparable in both groups (14.25 days vs. 14.48 days, p=0.267). Overall postoperative complications in group A and B were similar for number of cardiac (9.1 vs 7.7 %) and pulmonary (21.2 vs. 19.2 %) events respectively. The anastomotic leak rate in group A and B was 9 vs 7.7 % respectively. Incidence of postoperative chylothorax was however higher in group A (6.1 vs 1.9 %) while anastomotic stricture was lower (3.0 vs. 9.6 %) in group A. However the difference was not statistically significant (Table 2). We did not find any significant increase in perioperative mortality in patients undergoing surgery after induction therapy (3.0 vs. 5.8 %; p = ns).

Table 2 Comparison of postoperative parameters in group A and B

Surgical outcome	Group A	Group B	*P* value
Total operative time	343 min	335 min	0.157
ICU stay	6.35 days	6.47 days	0.314
Hospital stay	14.25 days	14.48 days	0.267
Cardiac events	6(9.1 %)	4(7.7 %)	0.529
Respiratory events	14(21.2 %)	10(19.2 %)	0.488
Chylothorax	4(6.1 %)	1(1.9 %)	0.265
Anastomotic leak	6(9.1 %)	4(7.7 %)	0.529
Anastomotic stricture	2(3.0 %)	5(9.6 %)	0.134
Perioperative mortality	5(7.5 %)	5(9.6 %)	0.653

Histopathological Outcomes

Almost 40 % of patients receiving preoperative therapy (chemotherapy or chemoradiation) showed a pathological complete response (pCR) to induction therapy on post-surgery histopathological assessment. Assessment of histopathological margins (proximal, distal and circumferential radial margin) suggested R0 resection in 97.0 % in group A and 95.9 % in group B. The mean number of mediastinal and abdominal lymph nodes retrieved were 9.3 and 11.5 in group A and 11.5 and 15.9 in group B respectively. Overall 62.5 % patients in group A and 50 % patients in group B were node negative pathologically (pN0). Comparison of PETCT done pre and post induction therapy, revealed significant response in 71 % patients with complete response in 49 % and nodal response in 68 %, which co-related with pathological complete response seen in 39 % and pathological nodal negativity of 62.5 % respectively (Table 3). Based on postoperative histopathology report; 43.75 % patients in group B patients required adjuvant therapy.

Survival Outcomes

Out of 118 patients, follow up data of 92 patients was available for outcome analysis. Overall and disease free survivals, calculated using Kaplan Meir curve, revealed statistically similar results in group A and B (Fig. 1) . However there was a trend

Table 3 Histopathology reports in group A and B

	Group A	Group B
pCR	26/66(39.39 %)	–
pN0	62.5 %	50 %
pN1	17.9 %	22.7 %
pN2	10.7 %	25.0 %
pN3	8.9 %	2.3 %
R0 resection	97.0 %	95.8 %

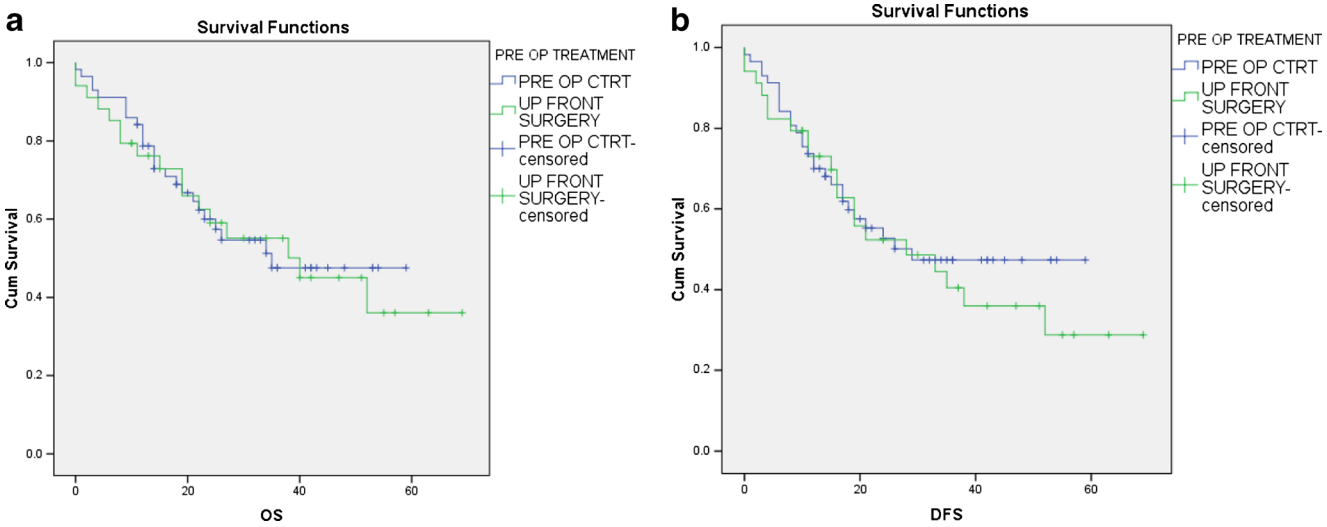

Fig. 1 Comparison of OS and DFS in group A and B

towards increase in DFS from 24 months and a better OS from 48 months in group A as compared to group B (p = ns) (Table 4).

There was no statisticall significant impact of tumour location, histologic subtype and clinical stage on DFS and OS, whereas pathological staging did affect the survivals (Table 5). Patients with pathologically negative nodes faired significantly better in terms of OS as well as DFS in both groups A and B (*p* value=0.027). Patients who had complete response had mean survival of 39.6 months as compared to 20.3 months in those with a poor response.

Discussion

The objective of preoperative concurrent chemoradiation is to increase overall and disease free survival by possibly treating micro metastasis and achieving better loco regional disease control. It may also act as a methodology for in vivo assessment of biologic behavior of the disease and plan further adjuvant therapy depending upon the clinico-radiologic and pathological response. Initial studies on preoperative chemo radiation, revealed survival benefit, but at the cost of morbidity and mortality. In the

Table 4 Comparison of OS and DFS in group A AND B

Months	Overall survival		Disease free survival	
	Group A	Group B	Group A	Group B
12	84.2 %	76.2 %	73.7 %	73.1 %
24	60 %	50.0 %	68.1 %	40.5 %
36	47.6 %	55.1 %	52.7 %	28 %
48	47.6 %	45.1 %	47.3 %	28.8 %
60	47.6 %	36.1 %	47.3 %	28.8 %

Table 5 Parameters affecting mean overall survival in group A and B

Parameters		Preop CTRT	Upfront surgery	P value
Age	<50 year	31.48	24.32	
	>50 year	39.80	43.98	0.572
Sex	Male	32.43	43.25	0.09
	Female	40.93	24.87	
Biopsy	SCC	38.61	41.62	0.474
	Adeno CA	24.94	31.9	
Location	Middle	37.39	38.71	0.727
	Lower	33.09	41.21	
	GEJ	32.75	29.37	
Clinical T stage	T1	–	–	0.468
	T2	26.00	38.00	
	T3	38.24	–	
	T4	27.00	–	
Clinical N stage	N0	28.35	31.0	0.381
	N1	39.00	41.5	
	N2	36.89	52.0	
Pathologic T stage	pT1	25.00		
	pT2	32.49		
	pT3	25.74		
	pT0	38.31		
Pathologic N Stage	pN0	41.47	48.66	0.027
	pN1	26.66	36.8	
	pN2	17.71	27.71	
	pN3	17.75	22.00	
Pathological Response	Complete	39.65	–	0.251
	Marked	30.66	–	
	Moderate	29.09	–	
	Poor	20.37	–	

meta-analysis by Florica et al. [13], increase in survival was offset by double postoperative mortality while Urshel and Vasant [14] suggested an increase in mortality, with benefit of preoperative therapy seen only after 3 years of treatment. In a study by Bossetet al [15] there was improvement in disease free survival with induction therapy in stage I and II, but low overall survival due to increase in postoperative mortality from 3.6 to 12.3 %.

In spite of dismal results in OS in most studies comparing preoperative therapy and surgery with surgery alone; the pathologic complete response rate was higher with preoperative chemoradiation than with preoperative chemotherapy alone (17–31 vs 2.5–8 %) respectively. Although there was no survival benefit due to increased perioperative mortality at that time [16, 17].

Further milestone in the evolution of esophageal cancer management was laid by the studies showing decreasing morbidity and mortality due to the advances in patient selection, perioperative and postoperative care [18]. CROSS trial revealed pCR rate of 29 % and a low inhospital mortality of 4 %, however increased overall survival, especially in squamous cell carcinoma [12]. Sjoquist et al., in their meta-analysis revealed absolute benefit in overall survival of 2 years in both squamous and adenocarcinoma and similar 30 day perioperative mortality [10].

There is limited experience of use of preoperative chemoradiation followed by radical esophagectomy in developing nations, mostly due to inacceptance by surgeons due to fear of increased perioperative mortality and morbidity, poor performance status and nutrition of patients; and in certain areas due to non-availability of resources and comprehensive cancer care facilities.

In our study, both groups were comparable in terms of age, sex and histologic subtype. Significant difference in tumor location could be explained by the tendency to consider mid thoracic tumors for induction therapy and lower esophageal tumors for upfront surgery. Group A had more advanced cases as clinically T2 patients were selected for upfront surgery in the initial period of the study. All patients received neoadjuvant therapy as planned and as reported in most of abovementioned studies. However, we used a different concurrent chemotherapy regimen (weekly cisplatinium) in our patients; instead of carboplatin and paclitaxel as used by the CROSS trial due to better treatment tolerance of concurrent cisplatin in our patients.

A statistically non significant, but slightly higher total operative time in group A suggests that surgery after induction therapy maybe somewhat more difficult especially in certain centers; but it is feasible and safe and can be performed without increasing the morbidity due to prolonged anesthesia. Similar ICU stay reflects comparable general condition, hydration status, maintenance of vitals, time to no intravenous fluid requirement, blood parameters and chest imaging and untoward events in the early postoperative period. Total hospital stay was also no different; pointing to same time for ICD removal, starting of oral feed and return to basic activities in patients undergoing surgery after induction therapy. Morbidity was not increased by induction therapy, as suggested by similar cardiopulmonary events and anastomotic leak rate. Fibrosis and loss of tissue planes account for higher number of chylothorax and more frequent stapled anastomosis account for lower stricture rate in group A though not significant. No increase in perioperative mortality corresponds to the latest studies showing survival benefit with chemoradiation not offset by toxicity.

Rate of pathological complete response and its survival benefit after neo-adjuvant therapy in our study, was similar to that observed in other studies [12]. Higher rate of pathological nodal negativity after induction therapy merits a special mention, as pN0 was the only factor to significantly alter the overall as well as disease free survival in both group A & B. R0 resection rates in locally advanced tumors patients (group A) highlights the benefit of induction therapy, though its significance for survival remains to be established. Comparison of overall and disease free survival in group A and B suggest that induction therapy not only narrowed the expected difference in survival due to selection bias (all early cases in group B), but also materialized into survival benefit after a few years (2 and 4 years for DFS and OS).

The tolerance and feasibility of chemo-radiation in the preoperative setting in esophageal cancer with trend to survival benefit, not being affected by postoperative morbidity or mortality requires further randomized studies with longer follow up data.

Conclusion

Radical esophagectomy after preoperative chemoradiation is feasible and safe even in developing nations with acceptable and comparable morbidity and mortality. Preoperative chemoradiation results in high rate of pCR, which correlates well with better loco regional control rates and survival across all patient groups and variable when compared to upfront surgery. However, randomized studies with longer follow up are required to substantiate our results and prove the survival benefit.

References

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0 (2013) Cancer incidence and mortality worldwide:IARC CancerBase N0.11(Internet). Lyon, France: International Agency for Research on Cancer; http:// globocan.iarc.fr. Accessed Dec 2013
2. A Project of National Cancer Registry Program. District wise Minimum Age Adjusted Incidence Rate per 1,00,000: http://www.canceratlasindia.org

3. DSouza N, Murthy NS, Aras RY (2013) Projection of burden of cancer mortality for India, 2011–2016. Asian Pac J Cancer Prev 14(7):4387–92
4. Parkin DM, Bray FI, Devesa SS (2001) Cancer burden in the year 2000. The Global picture. Eur J Cancer 37(8):4–66
5. Nygaard K, Hagen S, Hansen HS et al (1992) Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: a randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second Scandinivian trial in esophageal cancer. World J Surg 16(6):1104–9
6. le Prise E, Etienne PL, Meunier B et al (1994) A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus. Cancer 73(7): 1779–84
7. Apinop C, Puttisak P, Preecha N (1994) A prospective study of combined therapy in esophageal cancer. Hepatogastroenterology 41(4):391–3
8. Walsh TN, Noonan N, Hollywood D et al (1996) A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 335(7):462–7
9. Walsh TN, Grannell M, Mansoor S (2002) Predictive factors for success of neo-adjuvant therapy in upper gastrointestinal cancer. J Gastroenterol Hepatol 17:172–5
10. Sjoquist KM, Burmeister BH, Smithers BM et al (2011) Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable esophageal carcinoma: an updated meta-analysis. Lancet Oncol 12(7):681–92
11. Kelsen DP, Ginsberg R, Pajak TF et al (1998) Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 339(27):1979–84
12. van Hagen P, Hulshof MCCM, van Lanschot JJB et al (2012) Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 366:2074–84
13. Florica F, di Bona D, Schepis F et al (2004) Preoperative chemoradiotherapy for esophageal cancer: a systematic review and meta-analysis. Gut 53(7):925–30
14. Urschel JD, Vasan H (2003) A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. Am J Surg 185(6):538–43
15. Bosset JF, Gignoux M, Triboulet JP et al (1997) Chemoradiotherapy followed by surgery compared with surgery alone in squamous cell cancer of the esophagus. N Engl J Med 337(3):161–7
16. Burmeister BH, Smithers BM, Gebski V et al (2005) Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the esophagus: a randomized controlled phase III trial. Lancet Oncol 6(9):659–68
17. Stahl M, Walz MK, Stuschke M et al (2007) Preoperative chemotherapy versus preoperative chemoradiotherapy in locally advanced esophagogastric adenocarcinomas: first results of a randomized phase III trial. J Clin Oncol 25(18S):4511
18. Malthaner RA, Wong RK, Rumble RB et al (2004) Neoadjuvant or adjuvant therapy for resectable esophageal cancer: a systematic review and meta-analysis. BMC Med 2(1):35