Original Article

Concurrent Chemoradiotherapy followed by Surgery in Locally Advanced Squamous Cell Carcinoma of the Oesophagus: A Single Centre Experience

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Abstract

Introduction: Data on combined modality treatment for locally advanced squamous cell carcinoma of the oesophagus involving Asian patients are limited. Materials and Methods: A retrospective study of 56 consecutive patients with this condition treated with concurrent chemoradiotherapy followed by surgery in a single tertiary institution in Singapore was performed. Results: The median overall survival of the entire cohort was 14.1 months [95% confidence interval (CI); range, 8.6 to 19.6 months]. In patients who underwent successful oesophagectomy after chemoradiotherapy (n = 17), the median survival was 27.8 months compared to 9.8 months for those who did not have surgery (n = 39) (*P* = 0.046, log-rank test). The median time to first relapse for the entire cohort was 16.1 months (95% CI, 7.7 to 24.5 months). The time to first relapse was 23.9 months in the subgroup of patients with successful surgery and 12.1 months in the group which did not (*P* = 0.147, log-rank test). The high proportion of patients who were medically unfit for surgery or declined surgery may have conferred a selection bias. Conclusion: Concurrent chemoradiotherapy followed by surgery is feasible in selected patients. The benefit of adding of surgery to chemoradiotherapy is still controversial and we await the results of randomised controlled trials comparing chemoradiotherapy with surgery versus chemoradiotherapy alone.

Ann Acad Med Singapore 2005;34:369-75

Key words: Asian, Oesophagectomy, Retrospective study, Singapore

Introduction

Carcinoma of the oesophagus is a relatively uncommon malignancy in Singapore and incidence rates have been declining since 1968. A total of 506 cases were diagnosed from 1993 to 1997. The age-standardised rate for the same period was 5.8 per 100,000.[1] The predominant histologic type is squamous cell carcinoma, although there has been a shift towards adenocarcinoma histology in recent years in Western populations. The majority of patients present late in the course of disease, as a result of which long-term survival is poor. While concurrent chemoradiotherapy has been defined as the standard of care in unresectable non-metastatic disease,[2] controversy still exists in the setting of locally advanced but surgically resectable carcinoma of the oesophagus.

The 5-year survival rate ranges from 5% to 18% in several series for patients with locoregionally advanced (stage III) carcinoma of the oesophagus treated with surgery as the sole modality.[3-5] Attempts to improve these dismal results have generated numerous randomised trials studying the respective roles of preoperative radiotherapy, preoperative chemotherapy, preoperative combined chemoradiation, as well as postoperative radiotherapy.

The results of 3 randomised trials comparing concurrent

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chemoradiotherapy followed by oesophagectomy versus oesophagectomy alone have been published. Walsh and associates[6] treated 113 patients suffering from adenocarcinoma of the oesophagus with 2 cycles of preoperative 5-fluorouracil and cisplatin concurrent with radiotherapy and reported a significant improvement in median survival (16 months versus 11 months) ($P = 0.01$) and 3-year survival (32% versus 6%; $P = 0.01$) compared to surgery alone.

In a study by Urba et al,[7] 100 patients were randomised to preoperative cisplatin, vinblastine and 5-fluorouracil concurrent with radiotherapy. The predominant histology in this study was adenocarcinoma. A complete pathologic response was observed in 28% of patients. With a median follow-up of 8.2 years, the median survival was similar in both treatments (16.9 months versus 17.6 months for multimodal therapy and surgery respectively), and the improvement in 3-year survival (30% versus 16%) did not reach statistical significance.

A European study[8] included 282 patients with stage I or II squamous cell carcinoma of the oesophagus who were randomly assigned surgery alone or surgery preceded by chemoradiotherapy. Surgery was performed 2 to 4 weeks after the completion of the preoperative therapy. After a median follow-up of 55 months, preoperative treatment was associated with a higher frequency of curative resection, a significantly longer disease-free survival and time to local failure, and a lower rate of cancer-related deaths. However, there was no improvement in median survival (18.6 months in both groups). This study has been criticised because of inadequate radiation dose-fractionation schedule, and the use of single-agent cisplatin rather than multi-agent chemotherapy. While the results of neoadjuvant chemoradiotherapy followed by oesophagectomy are well reported in the Western literature, there are limited data regarding the outcomes of similar treatment regimens in Asian populations.

Between 1995 and 1999, the role of chemoradiotherapy followed by oesophagectomy was assessed at the Singapore General Hospital to address this issue. This report presented the results of such a treatment strategy for the entire cohort and also the separate results for patients who had chemoradiotherapy alone or chemoradiotherapy followed by surgery.

Materials and Methods

A retrospective study of concurrent chemoradiotherapy followed by oesophagectomy in 56 consecutive patients with locally advanced carcinoma of the oesophagus treated between September 1995 and September 1999 at the Singapore General Hospital, a tertiary care hospital in Singapore, was performed. Patients eligible for concurrent chemoradiotherapy during this period fulfilled the following criteria: age ≥21, histologically confirmed T3-4 N0-1 M0 (1983 American Joint Committee on Cancer Staging) squamous cell carcinoma of the oesophagus, performance status ≤2 (WHO criteria) with adequate renal, bone marrow and liver functions. Patients were not eligible if there was evidence of metastasis, tracheo-oesophageal fistula, or carcinoma of the cervical oesophagus. All patients underwent physical examination, chest X-ray, computed tomography (CT) scans of the chest and abdomen, oesophagoduodenoscopy, barium swallow, bronchoscopy and electrocardiogram prior to commencement of treatment. Endoscopic ultrasound was performed whenever possible.

Radiotherapy

The sequence of therapy is summarised in Figure 1. Radiotherapy was administered to a dose of 50 Gy (10 Gy per week in 5 fractions). Radiotherapy was begun on the first day of the chemotherapy. All patients were planned using 3D conformal techniques. The planned target volumes extended 5 cm beyond the longitudinal margins of the tumour defined by the endoscopic and radiologic findings, 1.5 cm beyond the radial margins. The radiation treatments were given in 2 phases with the initial Phase I delivered as parallel and opposed pair of fields. This was treated to a total dose of 40 Gy in 20 fractions of 2 Gy per fraction. The Phase II treatment was planned as a 3 fields technique aiming to spare the radiation dose to the underlying spinal cord. This would be delivered to an additional dose of 10 Gy in 5 fractions. All patients were treated daily except on weekends. If patients were deemed to have unresectable disease after reassessment or there were positive margins and/or viable tumour seen in the resected specimens in

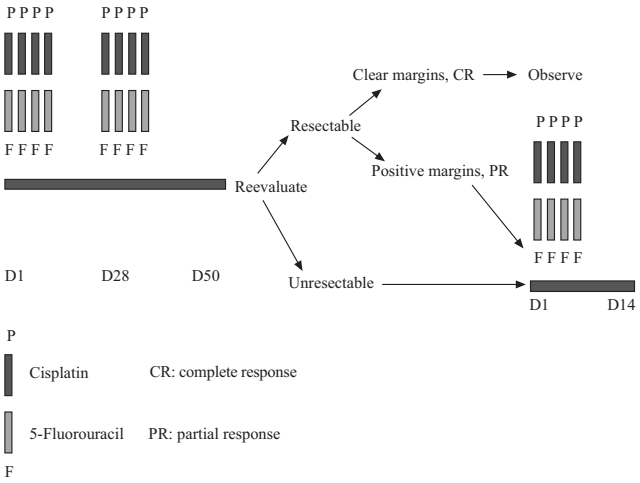

Fig. 1. Treatment flowchart.

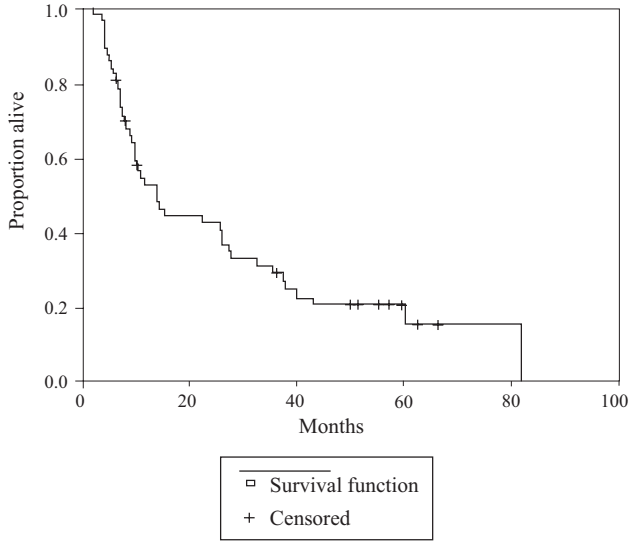

Fig. 2. Overall survival for entire cohort.

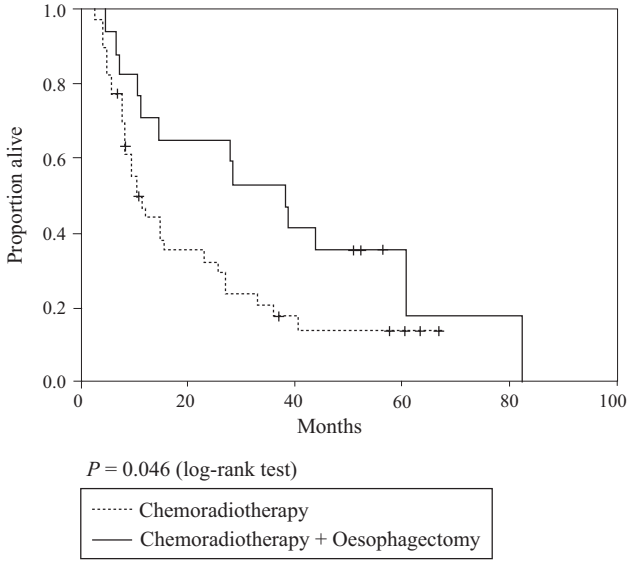

Fig. 3. Overall survival by treatment.

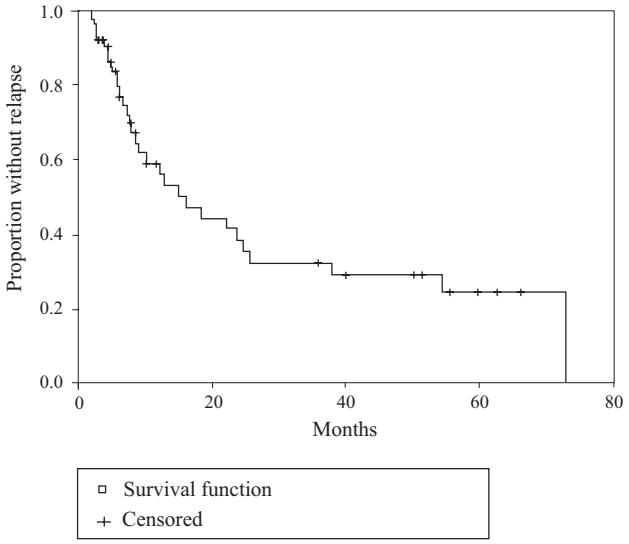

Fig. 4. Time to relapse for whole cohort.

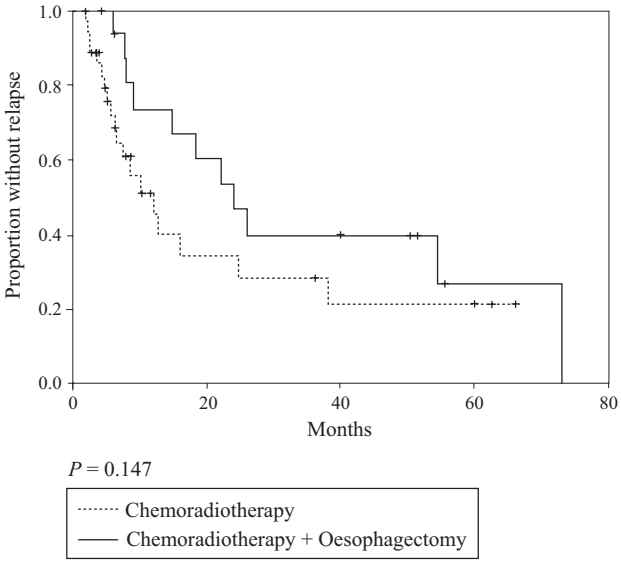

Fig. 5. Time to first relapse by treatment.

those who had surgery, they would receive an additional 14 Gy in 7 fractions to the Phase II treatment volume.

Chemotherapy

Chemotherapy was started on the same day as radiotherapy. Cisplatin 20 mg/m^2 was given with intravenous hydration over 6 hours on days 1 to 4, with mannitol and frusemide diuresis on day 1 while 5-fluorouracil 1gm/m^2 was given over 6 hours on days 1 to 4. Two courses of chemotherapy were given during radiotherapy at 4-week intervals. Three weeks after the completion of chemo-radiotherapy, a repeat evaluation was performed with CT chest, barium meal and oesophagoduodenoscopy. Patients deemed operable underwent transthoracic or transhiatal oesophagectomy. Patients with inoperable disease were given an additional cycle of the same chemotherapy concomitant with 14 Gy of radiotherapy in 7 fractions. Patients with operable disease underwent transthoracic or transhiatal oesophagectomy. If resection margin was positive or viable tumour was present in the resection specimen, patients were also treated with an additional cycle of the same chemotherapy concomitant with 14 Gy of radiotherapy in 7 fractions.

Clinical complete response was defined as the absence of visible tumour on CT scan, barium meal, oesophago-duodenoscopy and repeat biopsy. Pathological complete response was defined as the absence of viable tumour in the resection specimen on histopathologic examination.

Overall survival was calculated from time of diagnosis until time of death. Time to first relapse was calculated from time of diagnosis until the first documented relapse. In the event that death of relapse did not occur the observation was censored. Time to local relapse was calculated from time of diagnosis to time of documented locoregional recurrence, progression from clinical partial response or local progression while on chemoradiotherapy.

Statistical Analysis

Data analysis was performed using SPSS (Release 11.5). Survival curves for relapse-free and overall survival were calculated using the Kaplan-Meier method and compared using the log-rank test. Statistical significance was shown by $P < 0.05$.

Table 1. Patient Characteristics

Characteristics	All patients (n = 56) No. (%)	CRT (n = 39) No. (%)	CRT + S (n = 17) No. (%)
Age (y)			
Median	66	68	63
Range	43-84	43-84	47-75
Sex			
Male	44 (79)	30 (77)	14 (82)
Female	12 (21)	9 (18)	3 (18)
Race			
Chinese	55 (98)	38 (97)	17 (100)
Indian	1 (2)	1 (3)	0
Differentiation			
Well	4 (7)	3 (8)	1 (6)
Moderately	28 (50)	18 (46)	10 (59)
Poorly	10 (18)	7 (18)	3 (18)
Unknown	14 (25)	11 (28)	3 (18)
Site			
Upper	14 (25)	13 (33)	1 (6)
Middle	28 (50)	17 (44)	11 (65)
Lower	14 (25)	9 (23)	5 (29)
Performance status			
0	1(2)	1(3)	0
1	50 (89)	35 (90)	15 (88)
2	0	0	0
3	1 (2)	1 (3)	0
Unknown	4 (7)	2 (5)	2 (12)
Tumour stage			
T3	45 (80)	30 (77)	15 (88)
T4	10 (18)	8 (21)	2 (12)
Unknown	1 (2)	1 (3)	0
Nodal stage			
N0	36 (64)	27 (69)	9 (53)
N1	20 (36)	12 (31)	8 (47)
Endoscopic ultrasound	15 (27)	11(28)	4 (31)

CRT: chemoradiotherapy; S: successful oesophagectomy

Pretreatment characteristics of the patients are summarised in Table 1. The median age of the patients was 66 years (range, 43 to 84). There was a male preponderance and nearly all patients were Chinese. Ninety per cent of patients had performance status 0 to 1. Fifty-eight per cent of the tumours were well to moderately differentiated and 18% were poorly differentiated. Twenty-six per cent of the tumours were located in the upper third of the thoracic oesophagus while 49% and 25% were located in the middle and lower third respectively. Eighty-one per cent of tumours were staged as T3 and 18% as T4. Sixty-three per cent of patients were node-negative and 37% were node-positive.

A total of 119 cycles of chemotherapy concurrent with radiotherapy were administered to 56 patients. The median number of cycles per patient was 2 (range, 1 to 3). Three patients required interruption of radiotherapy for more than 1 week and 2 patients had interruption for less than 1 week.

The modalities of treatment received are summarised in Table 2. Seventeen patients (30%) underwent oesophagectomy after completion of chemoradiotherapy. Oesophagectomy was abandoned in 3 patients (5%) due to the presence of unresectable disease intraoperatively. Thirty-six patients (64%) received only chemoradiotherapy, of which 15 (42%) declined surgery while 21 (58%) where unfit for surgery. Most of these 21 patients where unfit due to poor baseline lung or cardiac function, although 7 patients in this group did not have surgery due to clinical disease progression.

Fifty-four patients were assessable for toxicity and the results are summarised in Table 3. No toxic deaths from chemoradiotherapy occurred. Ten patients (18%) developed grade 3 oesophagitis. Seventeen patients (32%) developed grade 3 or 4 neutropaenia, of whom 5 (29%) developed neutropenic fever. Four patients (7%) developed tracheo-oesophageal fistula, which were treated with oesophageal stents. There were 2 deaths after oesophagectomy. One patient had subcutaneous emphysema and pneumonia and passed away 37 days after surgery while the other patient developed pneumonia and passed away 15 days after surgery.

The response to chemoradiotherapy is summarised in Table 4. For the entire cohort, 25 patients (45%) had

Table 2. Treatment Received

Modality	No. (%)
Chemoradiotherapy followed by oesophagectomy	17 (30)
Chemoradiotherapy followed by attempted oesophagectomy	3 (5)
Chemoradiotherapy only	36 (64)

Table 3. Chemoradiotherapy Toxicity Graded by Common Toxicity Criteria (Version 2.0)

Toxicity	Grade 0 No. (%)	Grade 1 No. (%)	Grade 2 No. (%)	Grade 3 No. (%)	Grade 4 No. (%)
Anaemia	20 (37)	22 (41)	11 (20)	1 (2)	0
Neutropaenia	19 (35)	9 (17)	9 (17)	10 (19)	7 (13)
Oesophagitis	13 (24)	16 (30)	15 (28)	10 (19)	0
Sepsis	39 (72)	1 (2)	4 (7)	9 (17)	1 (2)
Thrombocytopaenia	34 (63)	15 (28)	5 (9)	0	0
TEF	52 (93)	-	-	4 (7)	0
Vomiting	35 (65)	9 (17)	8 (15)	2 (4)	0

n = 54 (2 patients not evaluable for haematological toxicity due to missing data)
TEF: tracheo-oesophageal fistula

Table 4. Response to Chemoradiotherapy

Response	All patients (n = 56) No. (%)	CRT (n = 39) No. (%)	CRT+S Clinical assessment No. (%)	CRT+S Path assessment No. (%)
Persistent disease	25 (45)	17 (44)	8 (47)	-
Clinical CR	19 (34)	10 (26)	9 (53)	-
Path PR	-	-	-	7 (41)
Path CR	-	-	-	10 (59)
PD	7 (13)	7 (18)	0	0
No data	5 (9)	5 (13)	0	0

CR: complete response; CRT: chemoradiotherapy; Path: pathologic; PD: progressive disease; PR: partial response; S: successful oesophagectomy

persistent disease and 19 (34%) had clinical complete response to induction chemoradiotherapy. Seven (13%) patients progressed while on treatment, mostly from progressive local disease although 1 patient had distant metastasis while undergoing chemoradiotherapy. Seventeen out of 56 patients eventually had successful oesophagectomy. In this select group of patients, 7 (41%) had residual tumour after induction chemoradiotherapy while 10 (59%) had pathologic complete response. Out of the 9 clinical complete responders to chemoradiotherapy who proceeded to have surgery, only 2 (22%) were found to have residual tumour in the oesophagectomy specimen.

The overall survival of the entire group is shown in Figure 2. The median overall survival was 14.1 months [95% confidence interval (CI), 8.6 to 19.6 months]. A log-rank test showed significant difference between patients with and without successful oesophagectomy ($P = 0.046$) (Fig. 3). In patients who underwent successful oesophagectomy after chemoradiotherapy, the median survival was 27.8 months, compared to 9.8 months for those who did not have oesophagectomy. In patients who had successful oesophagectomy after concurrent chemoradiotherapy, the log-rank test did not show any significant difference in terms of survival between patients who had pathologic complete response and those with residual disease ($P = 0.760$). The overall survival for patients with pathological complete response was 37.5 months, compared to 27.3 months for patients with residual disease.

Table 5. Pattern of First Relapse

Site of first relapse	All patients (n = 56) No. (%)	CRT (n = 39) No. (%)	CRT+S (n = 17) No. (%)
No relapse	23 (41)	17 (44)	6 (35)
Locoregional	11 (20)	10 (26)	1 (6)
Distant	13 (23)	6 (15)	7 (41)
Locoregional/distant	6 (11)	3 (8)	3 (18)
Missing data	3 (5)	3 (8)	0

CRT: chemoradiotherapy; S: successful oesophagectomy

Three patients were excluded from the time to first relapse analysis due to missing data. Table 5 summarises the pattern of first relapse. The median time to first relapse for the entire cohort was 16.1 months (95% CI, 7.7 to 24.5 months) (Fig. 4). A log-rank test failed to show any significant difference between patients with and without successful oesophagectomy ($P = 0.147$) (Fig. 5). In patients who underwent successful oesophagectomy after chemoradiotherapy, the time to relapse was 23.9 months, compared to 12.1 months for those who did not have oesophagectomy. In patients who had successful oesophagectomy after concurrent chemoradiotherapy, the log-rank test did not show any significant difference between patients who had pathologic complete response and those with residual disease ($P = 0.241$). The time to relapse for patients with pathological complete response was 54.3 months, compared to 14.8 months for patients with residual disease.

The median time to distant relapse was 27 months (95% CI, 8.6 to 45.3 months). A log-rank test did not show any significant difference between patients with and without successful oesophagectomy ($P = 0.742$). In patients who underwent successful oesophagectomy after chemoradiotherapy, the time to distant relapse was 27.0 months, compared to 38.0 months for those who did not have oesophagectomy. In patients who had successful oesophagectomy after concurrent chemoradiotherapy, the log-rank test did not show any significant difference between patients who had pathologic complete response and those with residual disease ($P = 0.489$). The time to distant relapse for patients with pathological complete response was 66.5 months, compared to 23.9 months for patients with residual disease.

The median time to local relapse for the entire cohort was 58.2 months. A log-rank test did not show any significant difference between patients with and without successful

oesophagectomy (P = 0.079). In patients who underwent successful oesophagectomy after chemoradiotherapy, the time to local relapse was 58.2 months, compared to 24.8 months for those who did not have surgery. In patients who had successful oesophagectomy after concurrent chemoradiotherapy, the log-rank test did not show any significant difference between patients who had pathologic complete response and those with residual disease (P = 0.126). The time to local relapse for patients with pathological complete response was 58.2 months, compared to 5.9 months for patients with residual disease.

Discussion

This retrospective review confirms the poor outcomes in patients with locally advanced carcinoma of the oesophagus. The median survival in our cohort of patients who had combined chemoradiotherapy without oesophagectomy was 9.8 months. This is somewhat shorter than that reported by al-Sarraf et al[2] and may reflect a small sample size or competing causes of survival in a population of patients with multiple comorbidities such as chronic obstructive lung disease. In the subgroup of patients who successfully completed both chemoradiotherapy and oesophagectomy the median survival was 27.8 months, which compares favourably with the results of other series.[6-8] This may again reflect small sample size, selection bias of a group of patients who were fit to undergo surgery or inclusion of patients with earlier stages of disease since only about one-third of patients had endoscopic ultrasound for staging.

Overall survival was significantly better in patients who underwent chemoradiotherapy followed by oesophagectomy compared to patients who received only chemoradiotherapy. However, this was not a randomised comparison. Conflicting results were reported in a randomised trial reported in abstract form: Stahl et al[9] found that surgery after chemoradiotherapy improved local control, compared with chemoradiotherapy alone, but did not prolong overall survival.

There was no statistically significant difference in time to first relapse, time to distant relapse or local relapse between the subgroup of patients who received chemoradiotherapy followed by surgery compared to those who had only chemoradiotherapy.

In patients who underwent oesophagectomy, no difference in outcome measures was seen between pathologic complete responders and those who had residual tumour. This may have been due to the small sample size of patients who had successful surgery. Concurrent chemoradiotherapy was well tolerated among this predominantly Chinese population, with neutropaenia occurring in 17 out of 54 patients who could be evaluated (31%), being the commonest grade 3 or 4 toxicity. There were no deaths from chemoradiotherapy toxicity. The 30-day mortality after oesophagectomy was 6% (1 out of 17). The ability to perform successful oesophagectomy was hampered by various factors including patient refusal, medical comorbidities such as chronic obstructive lung disease and development of progressive disease while on chemoradiotherapy in 7 patients (13%).

Many novel approaches in radiotherapy and chemotherapy are being tested in the clinical trial setting. Relatively new radiotherapy techniques such as three-dimensional conformal radiotherapy and brachytherapy[10] are associated with a more favourable toxicity profile but their role is not clearly established yet in the treatment of locally advanced oesophageal carcinoma. New taxane-based[11] and oxaliplatin-based[12] chemotherapy regimens are being used concurrently with radiotherapy, achieving promising results. Targeted therapies in the form epidermal growth factor receptor inhibitors have not been used concurrently with radiotherapy in the treatment of locally advanced oesophageal carcinoma, although phase I/II trials researching targeted therapies in the metastatic disease setting have been performed.

In conclusion, preoperative concurrent chemo-radiotherapy is feasible and tolerable although patient refusal and presence of comorbidities limit the number of patients who can undergo this form of combination therapy. The benefit of adding of surgery to chemoradiotherapy is still controversial and we await the results of randomised controlled trials comparing chemoradiotherapy with surgery versus chemoradiotherapy alone.

Acknowledgement

We thank Miss Charmaine Tan from the Medical Records Office for her assistance in the retrieval of case notes.

REFERENCES

1. Chia KS, Seow A, Lee HP, Shanmugaratnam K. Cancer incidence in Singapore 1993-1997. Singapore: Singapore Cancer Registry, 2000.
2. al-Sarraf M, Martz K, Herskovic A, Leichman L, Brindle JS, Vaitkevicius VK, et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J Clin Oncol 1997;15:277-84.
3. Orringer MB, Marshall B, Iannettoni MD. Transhiatal esophagectomy: clinical experience and refinements. Ann Surg 1992;230:392-400.
4. Ellis FH Jr. Standard resection for cancer of the esophagus and cardia. Surg Oncol Clin North Am 1999;8:279-94.
5. Chan WH, Wong WK, Chan HS, Soo KC. Results of surgical resection of oesophageal carcinoma in Singapore. Ann Acad Med Singapore 2000;29:57-61.
6. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 1996;335:462-7. Erratum in: N Engl J Med 1999;341:384.
7. Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A,

Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 2001;19:305-13.

8. Bosset JF, Gignoux M, Triboulet JP, Tiret E, Mantion G, Elias D. Chemoradiotherapy followed by surgery compared with surgery alone in squamous cell cancer of the esophagus. N Engl J Med 1997;337:161-7.
9. Stahl M, Wilke H, Walz MK, Seeber S, Klump B, Budach W, et al. Randomized phase III trial in locally advanced squamous cell carcinoma (SCC) of the esophagus: chemoradiation with and without surgery. Proc Am Soc Clin Oncol 2003;22:250 (abstr 1001).
10. Gaspar LE, Nag S, Herskovic A, Mantravadi R, Speiser B. American Brachytherapy Society (ABS) consensus guidelines for brachytherapy of esophageal cancer. Int J Radiat Oncol Biol Phys 1997;38:127-32.
11. Anne PR, Axelrod R, Rosato E, Rosato F, Kairys J, Ramirez M, et al. A phase II trial of preoperative paclitaxel, carboplatin, 5-FU and radiation in patients with resectable esophageal or gastric cancer. J Clin Oncol 2004;22:4031.
12. Giovannini M, Conroy T, François E, Seitz J, Boige V, Ducreux M, et al. Phase I study of first line radiochemotherapy (RCT) with oxaliplatin (Ox), fluorouracil (FU) and folinic acid (FA) in inoperable locally advanced (LA) or metastatic (m) esophageal cancer (EC). J Clin Oncol 2004;22:4044.