

● *Clinical Original Contribution***COMBINED MODALITY THERAPY FOR ESOPHAGEAL CARCINOMA:
PRELIMINARY RESULTS FROM A LARGE
AUSTRALASIAN MULTICENTER STUDY**

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Purpose: This report updates local control and survival experience and focuses on treatment toxicity in 294 patients with esophageal cancer who have been treated at six Australasian centers using three prospective unrandomized protocols that used concurrent radiation, cisplatin, and modest dose infusional fluorouracil. **Methods and Materials:** Protocol 1—"definitive" chemoradiation. One hundred and thirty-seven patients have been treated with "definitive" radiation to 60 Gy in 6 weeks plus two courses of cisplatin (80 mg/m²) and infusional fluorouracil (800 mg/m²/day over 4 days) during the first and fourth weeks of radiation. Protocol 2—"preoperative" chemoradiation and surgery. Seventy-eight patients received chemoradiation using the same chemotherapy, but 30-35 Gy in 3-4 weeks prior to surgery. Protocol 3—"palliative" chemoradiation. Seventy-nine patients deemed incurable were treated "palliatively" with the same chemoradiation protocol without surgery. Follow-up ranges from 6 months to 7 years (mean 22 months) in live patients.

Results: Durable palliation of dysphagia in all three treatment groups has been reflected by encouraging 3-year survival expectations of 43.2 ± 5% in definitively treated patients, 40.3 ± 7.65% in surgically treated patients, and 8.5% ± 3.9% in the palliatively treated patients. There are early indications that female patients have fared better than males. Toxicity levels were modest in all three groups. Following definitive treatment, severe myelotoxicity (World Health Organization grades 3 and 4) occurred in 19%, severe esophagitis (World Health Organization grade 3) in 11%, and moderate or severe benign stricture in 17%, depending upon age and sex of the patient (being worse in female patients).

Conclusions: These studies demonstrate that the concurrent addition of modest dose cisplatin and infusional dose fluorouracil to radiation in the definitive, preoperative, and palliative settings contribute to high rates of durable dysphagia-free survival, with overall survival comparable to (and possibly better than) the chemoradiation arm of the recently reported Intergroup Study, but at the cost of less morbidity.

Esophageal cancer, Combined modality therapy, Chemoradiation.

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INTRODUCTION

Concurrent chemotherapy and radiation has in recent times been reported by various centers as effective in the management of carcinoma of the esophagus (1–4, 6–13). The initial reports from Wayne State University in Detroit described a preoperative protocol using 30 Gy with cisplatin (CDDP) and infusional fluorouracil (FU) (8). These patients were then considered for surgery and in those resected, 24% of the pathologic specimen contained no tumor. This group of patients also had a significantly improved survival when compared to historical controls treated by surgery alone.

In 1987, Coia *et al.* (2) reported on a series of 50 patients treated with higher doses (50–60 Gy) with concurrent mitomycin C and infusional FU. High response rates at the primary site were noted and the need for resection questioned. More recently Herskovic *et al.* (10) have published the results of the prospective randomized intergroup trial comparing four courses of CDDP, infusional FU, and radiation, with radiation to 60 Gy alone. The combined modality arm experienced significantly improved disease-free and overall survival, but at the expense of considerable acute toxicity.

In Australasia, initial interest began at Royal Adelaide Hospital in 1984 using a preoperative protocol using radiation to 35 Gy with concurrent CDDP and infusional FU at significantly lower doses (500 mg/m²/day) than those used at Wayne State University (4). It was quickly realized that the protocol might be as effective as the Wayne State regimen in inducing complete histological response at the time of surgical resection. Unfortunately, calls for the instigation of controlled clinical trials comparing single with combined modality were unsuccessful at that stage. Following the formation of the Trans-Tasman Radiation Oncology Group (TROG), it had already become obvious that high response rates could also be achieved using doses of 60 Gy without surgery in adenocarcinomas, as well as squamous cell carcinomas (9). It was, therefore, decided to establish whether the promising Royal Adelaide Hospital experience could be reproduced with as little toxicity at other Australasian treatment centers using three prospective unrandomized protocols. The three protocols were based upon the Royal Adelaide protocols, namely, preoperative chemotherapy and radiation to 30–35 Gy in patients selected for surgery, definitive chemotherapy and radiation to 60 Gy in nonsurgical patients with limited stage disease, and palliative chemotherapy and radiation to 30–35 Gy in patients with metastases outside the tumor. By March 1994, seven centers had contributed a total of 294 patients to the protocols. The present report updates local control and survival experience with these protocols and focuses on toxicity in patients treated by chemoradiation alone.

METHODS AND MATERIALS

Patient selection

From July 1984 until March 1994, patients with biopsy-proven carcinoma of the esophagus and esophagogastric

junction of any histological subtype treated at seven institutions in Australia and New Zealand, were considered for combined modality therapy. Criteria for selection were as follows:

Protocol 1. “Definitive” radiation and chemotherapy: patients with disease localized clinically to the primary site and adjacent intrathoracic lymph nodes, including those who were technically inoperable, as well as those who were deemed unfit for surgery due to intercurrent medical conditions were considered for inclusion.

Protocol 2. “Preoperative” radiation and chemotherapy followed by definitive resection (known also in this report as the “surgical” group): patients with technically operable disease and medically fit for major surgery were considered for inclusion on this protocol. In all cases, surgery was performed with the intention of cure.

Protocol 3. “Palliative” chemotherapy and radiation: this protocol was considered for patients deemed incurable by any means due to the presence of extensive local invasion, nodal metastases outside of the thorax, and pulmonary or other systemic metastasis, but who were medically fit to receive chemotherapy. Prior to TROG participation in this study some patients with localized disease but with poor performance status were also treated with the palliative protocol.

Patients referred but medically unfit to receive the chemotherapy component of the protocol at the various centers were not treated on protocol and are not included in the present report. The most common reasons for exclusion were poor renal function, cardiovascular insufficiency, and advanced age associated with poor performance status.

Routine pretreatment evaluation of the patient included thorough clinical examination, full blood counts, serum biochemistry, liver function tests, barium swallow, esophagoscopy with biopsy, and computed technology (CT) scan of the chest and upper abdomen. Bronchoscopy was performed in all cases apart from those involving the lower third of the esophagus or esophagogastric junction. Further investigations were performed only when clinically indicated.

Treatment

The chemotherapy regimen consisted of CDDP 80 mg/m² given as a slow infusion over 1 h, preceded by suitable prehydration on day 1. This was followed by a continuous infusion of FU 800 mg/m²/day on days 1–5 over 96 h. In most cases, this required admission of hospital, but recently outpatient administration of chemotherapy into a central venous catheter with an electronically controlled pump has been possible. Patients treated preoperatively or for palliation received a single course of chemotherapy, while patients treated definitively with 60 Gy received a second course commencing on day 22.

Radiation commenced on day 1. Patients treated preoperatively or for palliation received midplane doses of 30–35 Gy in 15 fractions over 3 weeks using opposing ante-

rior and posterior linear accelerator portals. Field coverage included all macroscopically visible disease within the thorax, together with a margin of 5 cm of normal esophagus together with immediate draining lymph node groups. Patients treated definitively received 60 Gy given in 30 fractions over 6 weeks. It was recommended that the initial 30–35 Gy be given using anterior and posterior portals with coverage as described, with the balance using lateral or oblique arrangements, depending on the tumor location, to cover all macroscopic disease with a 3 cm margin, with an attempt made to restrict total spinal cord dose to 45 Gy. Planning was facilitated with CT scanning and lung tissue inhomogeneity correction for those receiving definitive treatment.

During the radiation treatment, patients were assessed weekly for symptoms and signs of acute toxicity. Particular attention was paid to nausea, vomiting, esophagitis, skin reactions, and bone marrow depression, with appropriate treatment being instituted where required. If marrow depression was evident immediately prior to the second course of chemotherapy, dose modifications ensued. Dietary supplements were frequently required and nasogastric feeding was instituted for those patients with grade 3 and 4 esophagitis or with significant weight loss. Parenteral nutrition was required in a few patients where severe obstruction did not permit nasogastric feeding. Assessment of acute toxicity was conducted using the system proposed by Dische for scoring irradiated tissues (5). The WHO system for grading of myelotoxicity was used to assess the effects of chemotherapy.

Patients treated preoperatively went on to planned resection 2–6 weeks after preoperative radiation and chemotherapy following endoscopic reevaluation of tumor response. Various procedures were performed according to tumor site, surgical preference, and extent of disease. The majority had an Ivor-Lewis resection using the stomach to reconstruct a conduit through the chest.

Follow-up assessment

Following therapy and formal endoscopic reassessment, patients were evaluated clinically every 3 months. The differentiation between benign and malignant stricturing following treatment was based on barium swallow and endoscopic and CT appearances. Although a tissue diagnosis was not obtained in every case, the diagnosis of benign stricture was not assumed until it had become obvious subsequently that disease progression was not taking place. The diagnosis of metastatic disease was made following clinical and radiological investigation of newly presenting symptoms. Kaplan-Meier estimates of overall survival, disease-free survival, and local disease-free survival have been used in this report. Local disease-free survival estimates have been derived from the date of first sign of recurrent disease. To quantify relief of dysphagia (and its durability) as a treatment end point, degree of dysphagia due to benign or malignant strictures was assessed at each follow-up visit on a scale: no impair-

ment; minor impairment requiring dietary alterations (e.g., change to soft solids or purees); and moderate or severe impairment requiring periodic dilatations or other procedures. The log rank test (Mantel-Haenszel) was used in subgroup comparisons. The RTOG/EORTC grading system was used in the assessment of late radiation effects.

RESULTS

Composition of the groups

The case composition according to a range of important prognostic variables of the three treatment groups is summarized in Table 1. The 78 patients proceeding to surgery following the preoperative schedule were slightly younger, enjoyed better performance status, and had lost less weight prior to treatment than the 137 patients treated by definitive radiation and chemotherapy alone. Although a greater proportion of patients treated surgically had adenocarcinomas (36% vs. 20%), there was no preponderance of lower third tumors among these patients. In addition, median tumor length was slightly greater, reflecting the presence of a greater number of T2 tumors.

The 79 patients selected for the palliative chemoradiation protocol were generally older, of worse performance status, and had a greater incidence of nodal both inside and outside of the thorax and systemic metastases than patients treated with definitive chemoradiation. It should be noted that six patients with nodal and systemic metastases went on to receive 60 Gy due to their youth and good performance status and have been included in the palliative group.

Survival and local control

Caution needs to be exercised when interpreting the survival curves shown beyond 3 years because appreciable censorship has occurred after this point. However, it will be noted from Fig. 1 that a small survival advantage in favor of the surgically treated patients (all histologies) noted in earlier reports (4, 7, 8) has disappeared by the end of the third follow-up year. At this stage, the projection for both groups is just above 40% ($40.3 \pm 7.65\%$ for surgically treated patients and $43.2 \pm 5.9\%$ for definitive chemoradiation patients). Figure 1 also shows that a small proportion of patients treated palliatively (with doses of 35 Gy or less) are also long-term survivors ($8.5 \pm 3.9\%$ at 3 years). Three of these patients remain disease free 5 years or more following treatment.

In earlier reports (7, 8), it was pointed out that adenocarcinomas were responding as frequently and as completely as squamous carcinomas to the preoperative schedule. Figure 2 indicates that disease-free survival is inferior in patients with adenocarcinoma, particularly in those selected for surgery ($p = < 0.001$). Separate analyses (not shown) suggest that relapse at the primary site and the development of distant metastases contribute

Table 1. Breakdown of the groups according to a range of variables that might influence treatment outcome

	Preoperative (n = 78)	Definitive (n = 137)	Palliative (n = 79)
All (years)			
median	63	68	69
range	34–77	36–91	37–96
Gender			
Male	58 (74.4%)	92 (67.2%)	50 (63.4%)
Female	20	45	29
Histology			
Squamous	49 (62.7%)	107 (79.3%)	55 (69.6%)
Adenocarcinoma	28	27	20
Undifferentiated	1	1	4
Site			
Upper third (incl. cervical)	7	26	9
Middle third	34	43	25
Lower third (incl. EG junction)	36 (46.75%)	66 (48.9%)	42 (55.26%)
Length (cms)			
median	6	5	5
range	2–11	1–15	2–16
Metastases			
No lymphadenopathy	71 (92.2%)	116 (84.7%)	56 (70.9%)
Intrathoracic nodes	1	9	11
Coeliac nodes	1	4	4
Other nodes	4	8	8
Systemic metastases	1 (0.7%)	0	25 (31.7%)
Performance status			
ECOG 0	51 (65.4)	57 (41.9%)	15 (19%)
ECOG 1	26	61	51
ECOG 2	1	18	13
Weight loss (kgs)			
median	3	5	6
(range)	0–22	0–31	0–25

EG = esophago-gastric.

ECOG = Eastern Cooperative Oncology Group grade.

equally to the high failure rate in patients with adenocarcinoma.

The greater complete pathologic response rate seen in female patients proceeding to surgery (Table 2) is echoed by better local relapse-free survival in female patients undergoing chemoradiation without surgery. Figure 3 suggests that female patients treated palliatively with 30–35 Gy experience only slightly inferior local disease-free expectations to male patients treated definitively to 60 Gy. At 2 years, female patients treated to 60 Gy have the highest projected local control rate of 70%. Very few male patients treated to 30–35 Gy remain relapse-free at the same stage, however. These differences in local control are reflected in differences in cause specific survival shown in Fig. 4.

Toxicity

Because surgical complications and mortality in patients from this series have been reported elsewhere (4, 7, 8) the present report has focused on early and late toxicity experienced by patients treated by chemoradiation alone. Table 3 provides an overview of acute and late toxicity and late complications (to date) experienced

by the 137 patients treated definitively according to sex and age. The table also summarizes the impact of toxicity experiences on dose delivery of both chemotherapy and radiation. From this table it is noted that female patients (both under and over 65 years) have experienced increased myelotoxicity and nausea and vomiting more frequently than male patients of the same age. Esophagitis during treatment has also been more frequent in female patients as has the development of posttreatment benign stricture. These increased toxicity levels have led to slightly more chemotherapy and radiation dose modifications in female patients over 65. Less obvious but similar trends to suggest that females experience more toxicity are also apparent in the palliatively treated patient group whose experience is summarized in Table 4. Two deaths are attributable to treatment toxicity with the definitive chemoradiation protocol. Both patients were elderly women who experienced severe esophagitis, malnutrition, hypomagnesaemia, and leukopenia during treatment and died shortly after completion of treatment.

Although two cases of possible radiation myelopathy listed in Table 3, the diagnosis of myelitis was not established in either. The first case occurred in a 68-year-old

ALL PATIENTS

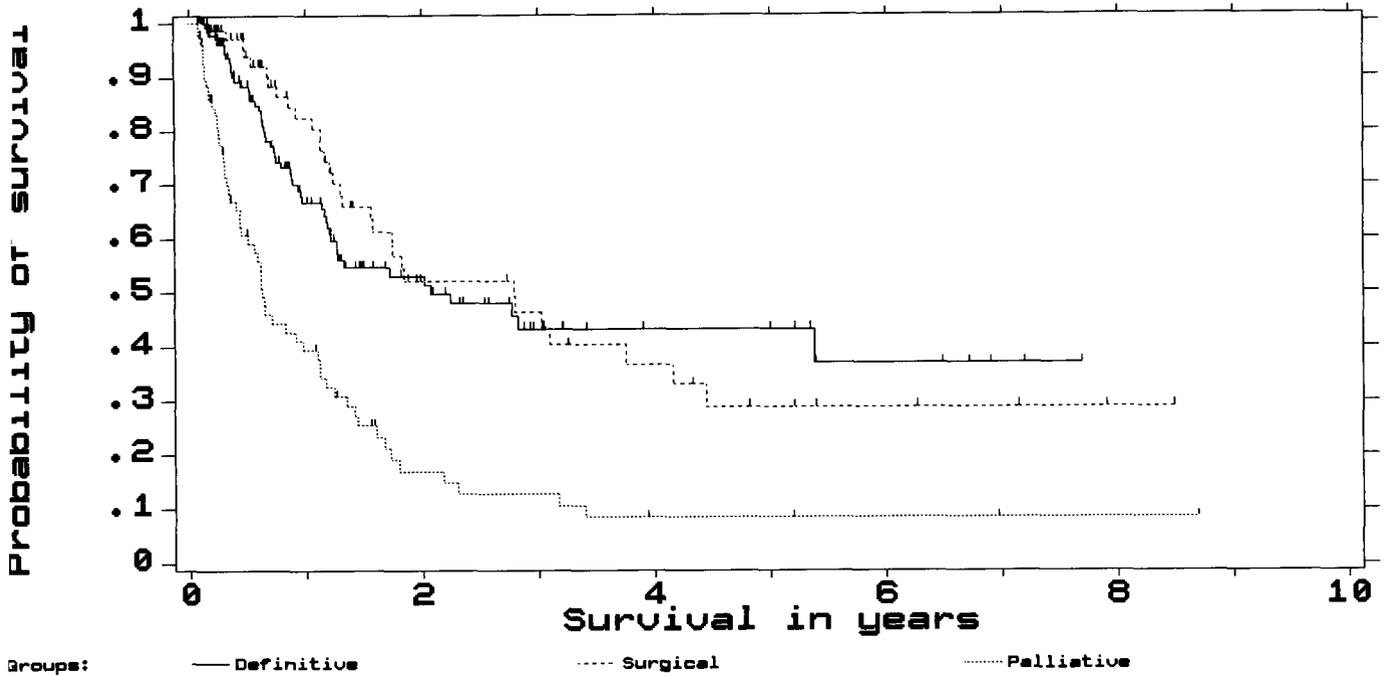


Fig. 1. Kaplan-Meier survival curves for the three treatment groups (definitive vs. palliative: $p = < 0.0001$; surgical vs. palliative: $p = < 0.0001$; 3-year survival probabilities: definitive— $43.2 \pm 5.9\%$; surgical— $40.3 \pm 7.65\%$; palliative— $8.5 \pm 3.9\%$).

female patient who had a tumor that was 12 cm in length. A total of 15 cm of spinal cord was irradiated to an intended dose of 37.5 Gy. The maximum dose to the cord

at the superior end of the portal was 51 Gy. Eleven months after treatment the patient developed symptoms and signs of spinal cord damage at a level corresponding to the

HISTOLOGY

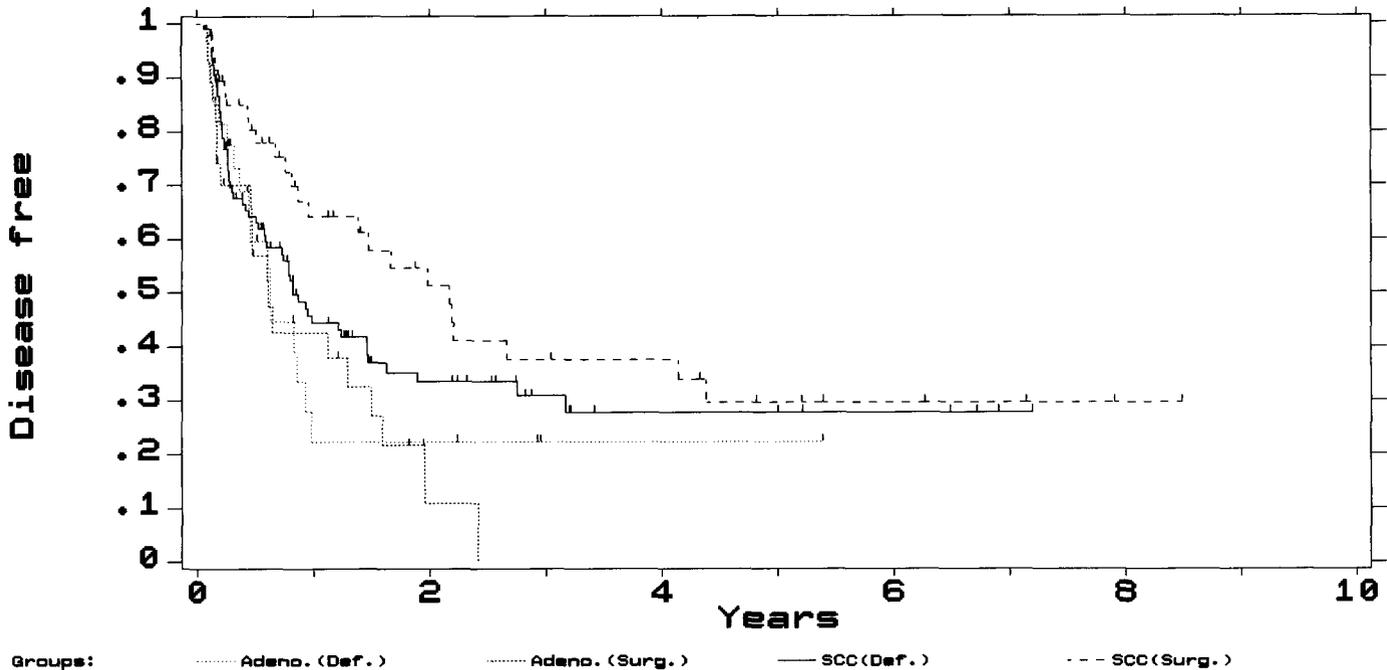


Fig. 2. Disease-free survival curves according to histological subtype in patients treated definitively and surgically (surgical group—SCC vs. adenocarcinoma: $p = < 0.0001$; definitive group—SCC vs. adenocarcinoma: $p = 0.42$).

Table 2. Histopathological response to the preoperative chemoradiation protocol in 73 patients proceeding to surgery where a detailed histological review is available

	No tumor in resected specimen	Residual tumor in resected specimen
Male ($n = 54$)	7 (13%)	47 (87%)
Female ($n = 19$)	7 (37%)	12 (63%)

radiation portals. This was associated with vertebral body collapse. At the same time she was noted to have disseminated disease in the form of lung metastases and was not considered suitable for surgical decompression. She died shortly afterwards and an autopsy was not performed. It was, therefore, not possible to ascertain with certainty as to whether the neurological sequelae in the setting were attributable to radiation, osteoporosis, or metastatic disease. In the second case, a male of 43 with a 6 cm tumor, L'Hermitte's syndrome developed 5 months after treatment. The syndrome resolved entirely after 4 months and the patient remains without neurological sequelae 10 months later. Maximum cord dose in this patient was estimated to be 46 Gy.

Dysphagia-free survival

Gender differences in posttreatment stricture rate have impacted on freedom from dysphagia (due to all causes) expectations. From Fig. 5 it is noted that patients selected for surgery enjoy significantly better freedom from moderate or severe dysphagia (due to benign or malignant

causes) than patients treated by high-dose chemoradiation alone ($p = < 0.003$), who, in turn, have slightly better expectations than patients treated palliatively ($p = 0.4$). However, it should be noted that the majority of moderate strictures occurring in nonsurgically treated patients were successfully managed by repeated dilatation. The curves, therefore, overstate differences in overall swallowing function between the groups.

Differences within the palliative chemoradiation group due to gender in favor of female patients ($p = < 0.04$, curves not shown) disappear in the definitively treated patients because the increased benign stricture rate observed in female patients in this group has offset the improved local control expectation observed in these patients. Gender considerations aside, however, Fig. 5 illustrates clearly that durable control of dysphagia occurs in a substantial proportion of patients treated palliatively.

It will be noted in Fig. 5 that the dysphagia-free survival estimates have utilized moderate or severe benign stricturing or any malignant stricturing as event end points. The reader is cautioned that many patients requiring periodic dilatation of moderate benign strictures enjoyed good swallowing function for much of their lives between dilatations. In addition, the curves shown do not provide an appreciation of milder degrees of swallowing dysfunction, particularly in the surgically treated group.

DISCUSSION

On the basis of the data presented, TROG feels that it has achieved its initial intention of confirming that the

LOCAL RELAPSE

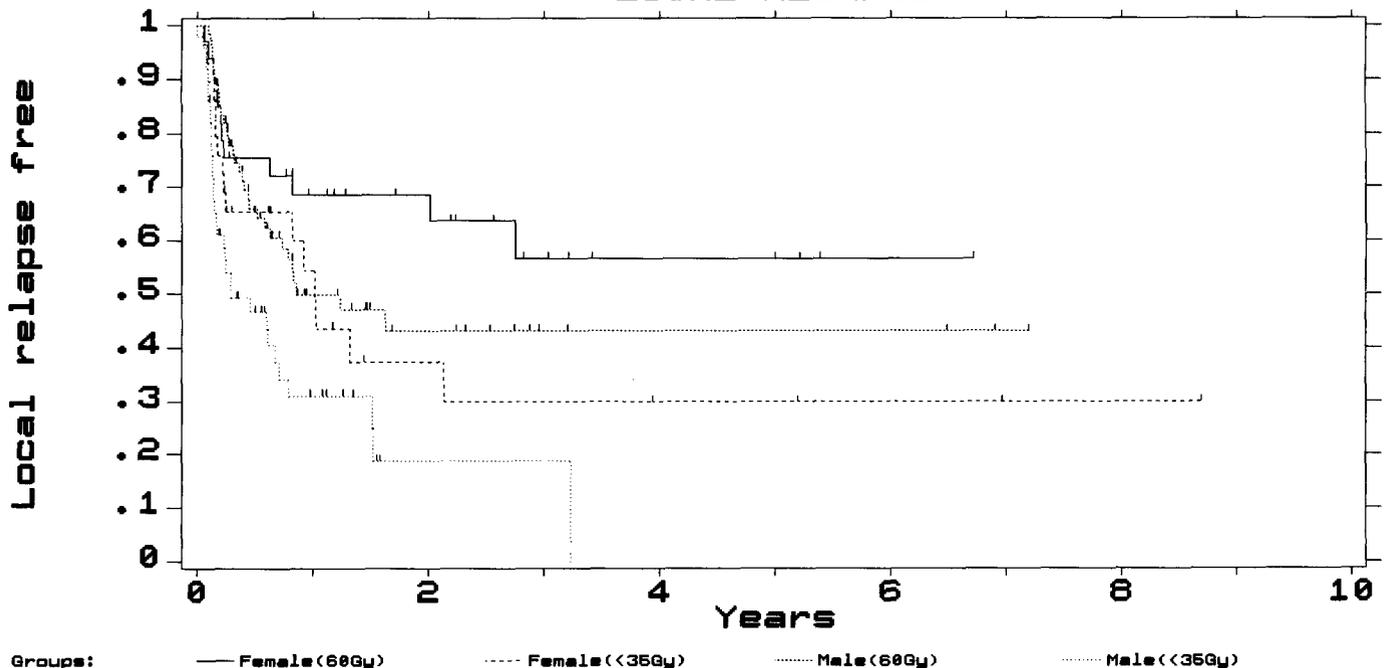


Fig. 3. Local relapse-free survival according to radiation dose in males and females (patients receiving 60 Gy—males vs. females: $p = 0.19$; patients receiving 35 Gy or less—males vs. females: $p = 0.07$).

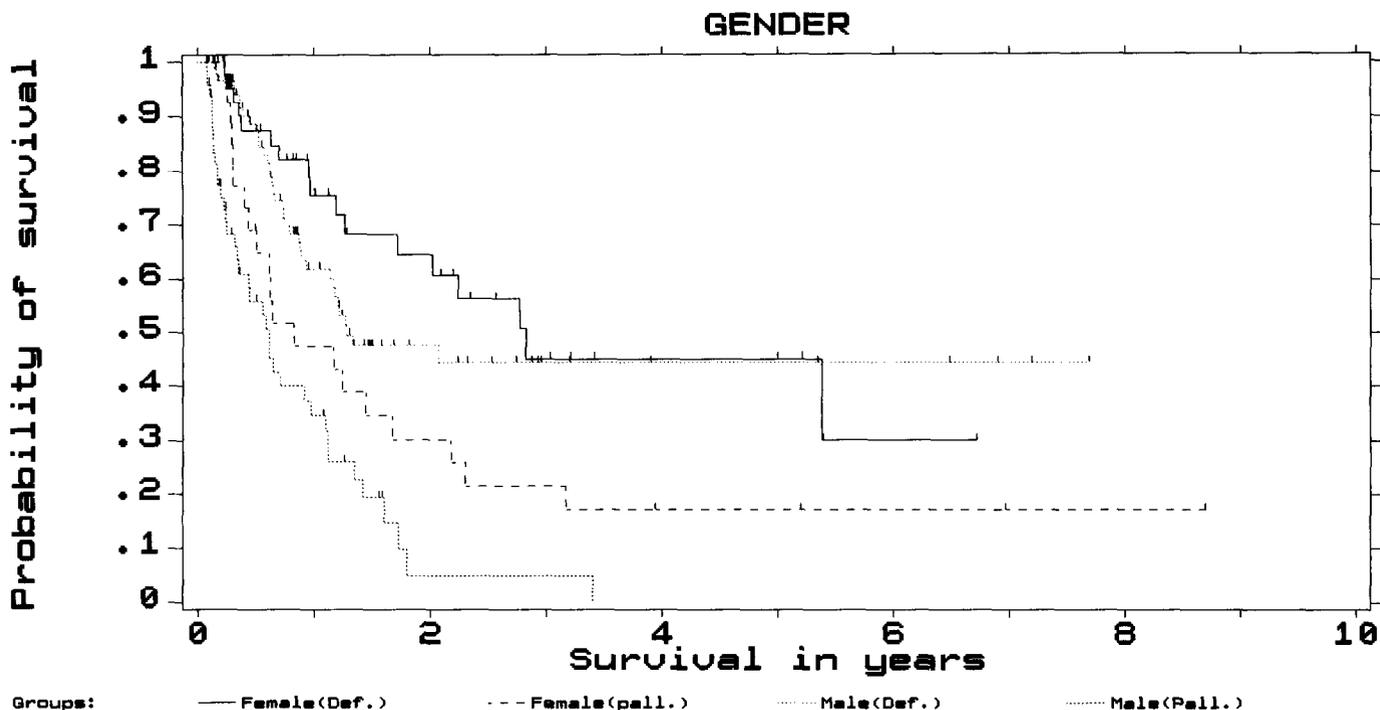


Fig. 4. Survival in males and females treated by chemoradiation only (definitively treated patients—males vs. females: $p = 0.35$; palliatively treated patients—males vs. females: $p = < 0.03$).

encouraging results produced at the Royal Adelaide Hospital can be transported to other Australasian centers without the expectation of prohibitive toxicity. Indeed, the toxicity rates observed in this series appear to be considerably lower than those reported from the combined modality arm of the Intergroup randomized trial (10). This protocol used four courses of CDDP (75 mg/m²) and infusional FU (1000 mg/m²), two of which were given during a course of radiation that stopped at 50 Gy. Forty-eight percent of patients treated on this protocol were reported to have experienced severe life-threatening myelotoxicity, while 33% experienced severe or life threatening upper gastro-intestinal side effects. Although the definitive protocol that is the subject of this report used higher radiation dosage, only two courses of chemotherapy were given with FU dosage restricted to 800 mg/m²/day. These differences may be sufficient to account for the differences in the toxicity profiles reported. Of considerable interest is the possibility that the regimen used in Australasia might have greater antitumor activity than the Intergroup protocol. Survival in the combined modality arm of the Intergroup trial was 38% ($\pm 14\%$) at 24 months, whereas the corresponding percentage for patients treated definitively in the present study was 51.4% ($\pm 5.3\%$). Clearly, further controlled studies are necessary to define optimal permutations of radiation and chemotherapy dosage.

The proportion of patients with metastases who were treated with palliative chemoradiation in this study and who experienced permanent relief of their dysphagia is noteworthy. The cost to these patients in terms of toxicity

was very modest. In the past, many such patients were immediately intubated, but at TROG centers this practice has now virtually ceased (7). Palliative chemoradiation has, therefore, provided a very timely expansion of the range of options available at the TROG centers for managing this sizeable subgroup of patients with esophageal cancer.

Surgical resection of esophageal cancer is often justified on the basis that, despite the fact that it is a major undertaking associated with a small but appreciable mortality and produces very few cures, it does permanently relieve dysphagia in the majority of patients. It is pointed out by its proponents that dysphagia causes very significant misery, almost completely destroying the quality of the patients remaining life, and that its relief is a major boon for the patient. Many patients with esophageal cancer, however, are beyond surgery due to advanced age and intercurrent illness. This report demonstrates that a significant proportion of patients who are unsuitable for surgery and treated by definitive chemoradiation have remained permanently dysphagia free without recourse to repeated dilatations. In addition, there is now good reason to hope that many of these patients will be cured without recourse to surgery. The Trans-Tasman Radiation Oncology Group is currently examining the role of "prophylactic" posttreatment dilatation, as advocated by Coia *et al.* (3), to see whether this procedure will reduce the incidence of benign stricture. The question will be asked whether preoperative chemoradiation improves upon the results achieved with surgery by itself. Of course, no answer can come from an unrandomized study such as

Table 3. Treatment-related toxicity and dose reductions according to gender and age in the definitively treated patient group

	Definitive group (n = 137)			
	Males (n = 92)		Females (n = 45)	
	Under 65 (n = 43)	Over 65 (n = 49)	Under 65 (n = 13)	Over 65 (n = 32)
Myelotoxicity Grade				
1	6	9	1	4
2	6	4	4	9
3	3 (21%)	9 (30.6%)	1 (54%)	8 (56%)
4	0	2	2	1
Sepsis	0	0	0	1
Nausea and vomiting grade				
1	12	12	3	6
2	10	5	6	12
3	3 (30%)	8 (26.5%)	2 (61.4%)	5 (53%)
Diarrhea	0	7 (14.3%)	2 (17%)	1 (3.2%)
Chemotherapy				
1st cycle				
reduced	3 (7%)	5 (10.2%)	1 (7.7%)	2 (6.4%)
omitted	0	0	0	0
2nd cycle				
reduced	4 (9.3%)	10 (20.4%)	3 (23.1%)	6 (19.2%)
omitted	0	5 (10.2%)	1 (7.7%)	4 (12.8%)
Esophagitis grade				
1	7	6	1	6
2	11	11	3	12
3	2 (30%)	7 (36.6%)	4 (54%)	2 (44.8%)
Posttreatment stricture				
Mild	3	3	3	7
Moderate	6	5	3	3
Severe	1 (16%)	0 (10%)	1 (31%)	4 (22%)
Acute pneumonitis	1 (2.3%)	1 (2%)	0	0
Pulmonary fibrosis	3 (7%)	0	0	2 (6.4%)
Myelopathy	1 (2.3%)	0	0	1 (3.2%)
Radiation dose				
60 Gy or more	33 (76.6%)	40 (81.6%)	10 (78%)	23 (73.4%)
50–59 Gy	5	4	2	4
Under 50 Gy	5	5	1	5

Criteria for grading:

Myelotoxicity—(Leukocytes) grade 1: 3–3.9; grade 2: 2–2.9; grade 3: 1–1.9; grade 4: < 1.0.

Nausea and vomiting—grade 1: nausea only; grade 2: transient vomiting; grade 3: prolonged vomiting requiring medication; grade 4: Intractable uncontrolled vomiting.

Esophagitis—grade 1: Discomfort, no dietary disturbance; grade 2: persistent discomfort requiring medication and dietary modification; grade 3: severe discomfort requiring nasogastric, parenteral or gastrostomy feeding.

Stricture—mild: easily dilated or dilatation unnecessary; moderate: regular dilatation necessary for continuing dysphagia; severe: dysphagia not satisfactorily managed by dilatation.

this one. The Trans-Tasman Radiation Oncology Group is encouraged by the surgical results achieved and has now activated a randomized trial comparing preoperative chemoradiation and surgery with surgery alone in Australasia. The results will complement those already in progress.

Clearly, many factors can impact on local control and survival, and bias results in patient groups selected for treatment on the basis of physician choice. Considerable caution, therefore, needs to be exercised when interpreting the results presented, particularly those from subgroup analyses. For example, the convergence of the survival curves for patients treated surgically and for patients treated with definitive chemoradiation might be due to

the increased presence of patients in the surgical group who fared poorly due to factors other than the efficacy of treatment itself. Survival was worse in patients with adenocarcinoma, particularly in patients treated surgically. It is possible that larger, bulkier tumors were more frequently present in this subgroup of patients. However, this may not be the only explanation, and the issues of durability of response and the rate of development of metastases in patients with adenocarcinoma deserve continuing attention as accrual increases. Another finding that requires cautious interpretation is the difference in response noted according to gender. These differences, however, did appear coherent, which could suggest that real differences are present. The observation that female

Table 4. Treatment-related toxicity and dose reductions according to gender and age in the palliatively treated patient group

Palliative group (n = 79)		
	Males (n = 50)	Females (n = 29)
Myelotoxicity Grade		
1	17	10
2	4	5
3	8 (38%)	3 (41%)
4	7	4
Sepsis		
	0	0
Nausea and vomiting Grade		
1	11	7
2	14	12
3	2 (32%)	0 (41%)
Diarrhea		
	4 (8%)	1 (3%)
Chemotherapy		
1st cycle		
Reduced	3 (6%)	3 (10%)
Omitted	0	0
2nd cycle		
Reduced	5 (10%)	5 (17%)
Omitted	19 (38%)	11 (38%)
Esophagitis Grade		
1	9	11
2	9	5
3	2 (22%)	2 (24%)
Posttreatment stricture		
Mild	3	1
Moderate	1	3
Severe	0 (2%)	0 (10%)
Acute pneumonitis		
	0	0
Pulmonary fibrosis		
	0	1 (3%)

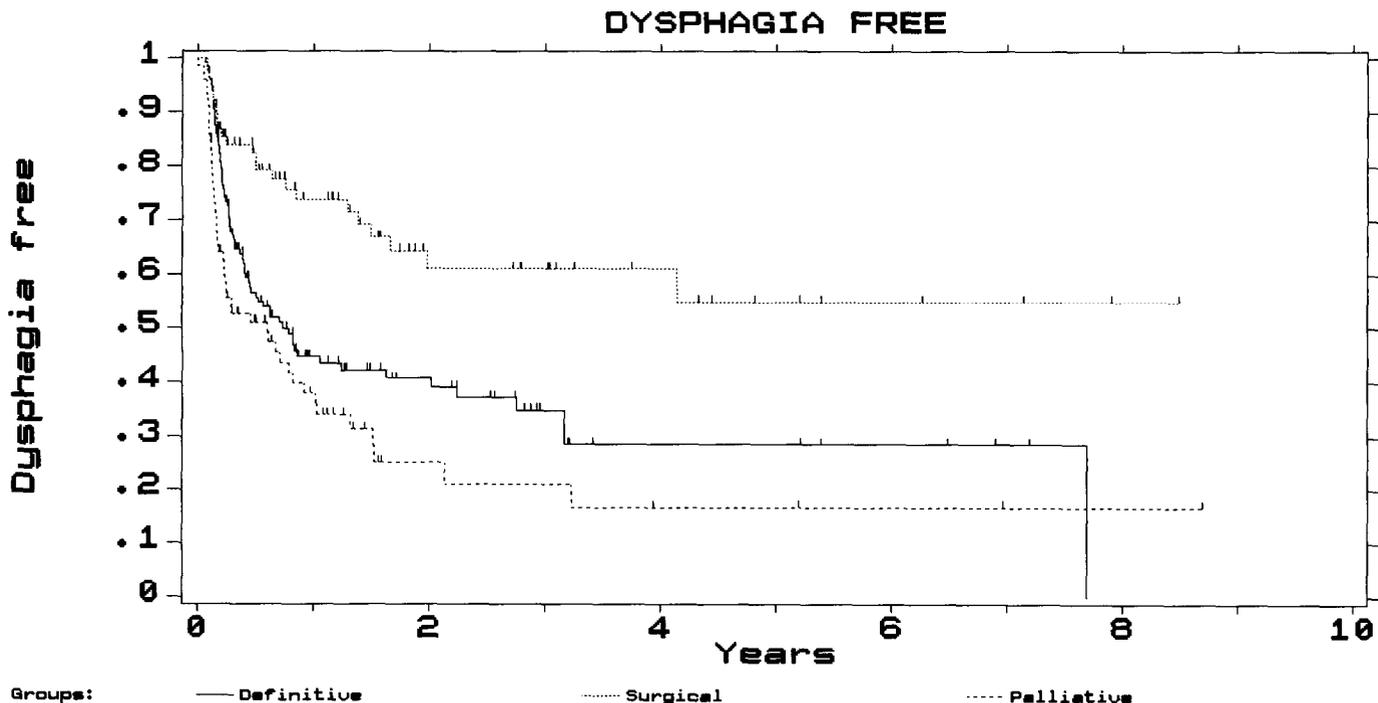


Fig. 5. Dysphagia-free survival according to treatment group. Dysphagia-free survival is defined as freedom from either local recurrence or from moderate or severe benign stricturing requiring repeated dilatations or other procedures (the reader is cautioned that the curves do not reflect the proportions maintained "dysphagia free" by repeated dilatations) (surgical vs. definitive groups: $p = < 0.0003$; definitive vs. palliative groups: $p = 0.04$).

patients experience more toxicity but are rewarded with superior local control and survival expectations would be of considerable interest if confirmed by additional data. Better survival has been observed in female patients following treatment of tumors of the esophagus (13) and at many other sites, but increased toxicity is an infrequently documented price for females to pay for their good fortune!

CONCLUSIONS

1. The encouraging results produced at Royal Adelaide Hospital with a regimen that is associated with very

modest toxicity have been reproduced by other centers in Australasia. The toxicity experienced by patients treated with the definitive chemoradiation protocol appears to be less than that associated with the Intergroup combined modality treatment arm, but efficacy may be comparable or better.

2. The palliative regimen used has produced excellent palliation of dysphagia at the cost of little toxicity in a worthwhile percentage of patients who have presented with metastatic disease.
3. There are early indications, which await confirmation, that female patients experience more toxicity, but are rewarded with better local control and survival expectations.

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