GENERAL THORACIC SURGERY

INDUCTION THERAPY FOR ESOPHAGEAL CANCER WITH PACLITAXEL AND HYPERFRACTIONATED RADIOTHERAPY: A PHASE I AND II STUDY

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Objective: Induction chemoradiotherapy followed by surgery may improve survival rates among patients with esophageal carcinoma. We designed a novel intense induction regimen with paclitaxel and high-dose hyperfractionated radiotherapy to maximize complete response rates. **Methods:** Forty patients with esophageal cancer were treated in a phase I and II trial of induction chemotherapy (cisplatin, 5-fluorouracil, and paclitaxel) at three dosage levels (75, 125, and 100 mg/m²) and concurrent hyperfractionated radiotherapy (45 Gy to the mediastinum, 58.5 Gy to the tumor). The mean age was 62 years, and 32 patients (80%) had adenocarcinoma. Twenty-eight of 40 (70%) patients had locally advanced tumors (T3, or stage IIB or greater). **Results:** The average hospitalization for induction treatment was 17 days. Toxicity was substantial, with esophagitis necessitating nutritional support the most common complication. The maximum tolerated dose of paclitaxel was 100 mg/m². Two patients died during induction treatment. Thirty-six patients (90%) underwent resection. The median length of stay was 10 days, and two patients died after the operation. Fourteen of 36 patients (39%) had a pathologic complete response. Patients who received all prescribed chemotherapy had a higher pathologic complete response rate (50%) than did patients who required dose reduction (17%; $p = 0.076$). The 2-year survival rate was 61% (95% CI 35% to 86%) with a median follow-up of 11.9 months. **Conclusions:** Paclitaxel at a dose of 100 mg/m² appears to have acceptable toxicity. The high pathologic complete response rate in this regimen is encouraging, but it is associated with substantial toxicity. The toxicity of this regimen is not acceptable and will require substantial reduction in the radiation component. Survival data are too short-term to confirm enhanced survival. (J Thorac Cardiovasc Surg 1997; 114:811-6)

Multimodal therapy of esophageal carcinoma appears to increase survival. The addition of chemotherapy (cisplatin and 5-fluorouracil) to radi-

ation therapy increased survival compared with radiation alone in a randomized trial reported by Herskovic and colleagues.¹ Walsh and associates² recently reported that multimodal therapy (cisplatin, 5-fluorouracil, and radiation therapy) followed by surgical resection improves survival compared with surgical treatment alone. The optimal regimen remains unknown. Previous reports emphasize the importance of a high pathologic complete response rate, because patients with high rates have enhanced survival rates.^{2,3} Paclitaxel is a new agent with high response rates in metastatic esophageal cancer, and it can also act as a radiation sensitizer.^{4,5} We designed an intensive induction program that included paclitaxel and high-dose hyperfractionated radiotherapy in an effort to maximize pathologic complete response rates, potentially improving survival rates.

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Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Cisplatin	C	C	C	C	C																							
5-FU	F	F	F	F	F																							
Paclitaxel	T																											
XRT	✓	✓	✓	✓	✓			✓	✓	✓	✓	✓			✓	✓	✓	✓	✓			✓	✓	✓	✓	✓		
	✓	✓	✓	✓	✓																							

Day	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	62
Cisplatin	C	C	C	C	C																						R	S
5-FU	F	F	F	F	F																							
Paclitaxel	T																											
XRT	✓	✓	✓	✓	✓																							
	✓	✓	✓	✓	✓																							

<u>Paclitaxel Dose Escalation</u>	
<u>Level</u>	<u>Dose (mg/m2)</u>
1	75
2	125
3	100

C =cisplatin 20mg/m2/d
5-FU =5-Fluorouracil 800 mg/m2/d by continuous infusion
P =Paclitaxel per schema given over 3 hours
✓ =XRT (pre-op dose = 58.5Gy to tumor; 45 to elective volume)
R =Restaging
S =Surgery

Paclitaxel Dose Escalation	
Level	Dose (mg/m ²)
1	75
2	125
3	100

Fig. 1. Treatment schema.

Patients and methods

Patient population. From April 1995 to February 1997, 77 patients were seen at the Massachusetts General Hospital Thoracic Oncology Center with newly diagnosed esophageal cancer. All patients with potentially resectable esophageal cancer were encouraged to enter this phase I and II trial of multimodal therapy. Eligibility criteria included resectable esophageal cancer, T1 through T4 disease, N0 through N1 disease, bilirubin level of 2.0 mg/dl or less, creatinine level of at least 2.0 mg/dl, platelet count of at least 75,000 cells/mm³, white blood cell count of more than 2500 cells/mm³, age older than 18 years, performance status of less than 2 (Eastern Cooperative Oncology Group), and signed informed consent. Exclusion criteria included distant metastatic disease, previous chemotherapy, previous radiotherapy, uncontrolled infection, T1N0 lesions, and bulky disease not encompassable by a safe radiation port. Forty patients were entered into this trial. Thirty-seven others were deemed ineligible for the following reasons: distant metastases, nine; required radiation port too large, eight; medical comorbidities, seven; unresectability, four; patient refusal, four; previous cancer treatment, three; and T1N0 lesion, two. The study was approved by the Human Studies Committee, and written informed consent was obtained from all participants.

Staging. All patients underwent screening for distant metastatic disease, with a computed tomographic scan of the chest, upper abdomen and brain along with a bone scan. Esophagoscopy with endoscopic ultrasonography was performed to assess the local extent of the tumor. The tumor stage was defined according to the classification of the American Joint Committee on Cancer.⁶

Chemotherapy. Chemotherapy consisted of two courses of cisplatin, 5-fluorouracil, and paclitaxel 4 weeks apart. Cisplatin (20 mg/m²) was infused for 1 hour on days 1 to 5. The 5-fluorouracil (800 mg/m²/day) was given as a continuous infusion on days 1 to 5. Paclitaxel was given for 3 hours according to a dose escalation schema (75, 125,

and 100 mg/m²). Fig. 1 illustrates the treatment schema. Paclitaxel at 75 mg/m² was chosen empirically. Initially, only three patients were to be treated at this level, but a stroke and paclitaxel anaphylaxis occurred in patients 2 and 3, prohibiting accurate assessment of toxicity. Accordingly, three additional patients were treated at this dose level. The dose was then escalated to 125 mg/m² (again empirically chosen), and three patients were treated. A myocardial infarction thought to be related to the 5-fluorouracil developed in the third patient (with known coronary disease) during the first cycle of treatment. The second cycle was therefore omitted. Accordingly, one additional patient was treated at this dose level. We determined that paclitaxel at 125 mg/m² was greater than the maximum tolerated dose (75% grade 4 toxicity; one myocardial infarction and fever and neutropenia in two patients) and chose 100 mg/m² as the next dose level. The first three patients treated with paclitaxel at 100 mg/m² tolerated chemotherapy well, without neutropenia or other significant complications.

Radiation therapy. This study employed a concurrent boost technique in which the initial volume (gross tumor and elective volume) was treated once a day and the boost volume (gross tumor) was also given a concurrent boost for 10 days on a twice daily schedule. A total dose of 45 Gy was delivered in 25 fractions through 5 weeks (180 cGy/fraction) to the original volume. An additional dose of 13.5 Gy was given in 10 fractions by delivering 135 cGy in the morning on the first of the twice-daily treatment schedule for the first 5 days and last 5 days to the gross tumor during continuous 5-fluorouracil infusion. The gross tumor therefore received 58.5 Gy and was in the field that was to be resected. The area of esophagus that was to be anastomosed to the stomach received 45 Gy, which was thought to be a "safe" dose to allow healing. This intensive dose was chosen to maximize the chance for a complete resection and complete response.

Surgery. After induction treatment, patients were restaged with a computed tomographic scan of the chest

Table I. Complications of chemotherapy according to paclitaxel dose

Cycle	Complication	75 mg/m ² (n = 6)		125 mg/m ² (n = 4)		100 mg/m ² (n = 30)	
		No.	%	No.	%	No.	%
1	Nadir ANC	1477		790		1370	
	GF	2/6	33	2/4	50	6/28	21
	G4E	0		3/4	75	12/28	43
2	Nadir ANC	847		1200		1036	
	GF	2/6	33	1/2	50	7/28	25
	G4E	3/6	50	2/2	100	16/28	57

ANC, Absolute neutrophil count; GF, granulocytopenic fever; G4E, esophagitis necessitating enteral or parenteral nutrition.

Table II. Influence of chemotherapy dose reduction on pathologic complete response rate

	PCR		p Value
	No.	%	
Complete chemotherapy	12/24	50	0.076
Reduced chemotherapy	2/12	17	

PCR, Pathologic complete response.

Table III. Influence of histology on pathologic complete response rate

Histology	PCR		
	No.	%	p Value
Squamous cell carcinoma	4/6	67	0.18
Adenocarcinoma	10/30	33	

PCR, Pathologic complete response.

and upper abdomen. Resection was undertaken if there was no evidence of unresectability on the restaging scan. Resection was planned for day 62 but was delayed if necessary to allow the patient to recover sufficiently from induction treatment. A left thoracoabdominal approach was generally used for low-lying lesions, and an Ivor Lewis approach was used for higher lesions.

Statistical methods. Survival was measured from the date of first therapy to the date of death or most recent follow-up visit. Actuarial survival was calculated with the Kaplan-Meier method. Fisher's Exact Test was used to determine whether a relationship existed between two nominal variables.

Results

Forty patients were entered into this trial, 35 men and five women. Thirty-eight patients were white and two were black. The mean age was 62 (33 through 76) years, and 10 patients were 70 years old or older. Thirty-two patients (80%) had adenocarcinoma, seven (17.5%) had squamous cell carcinoma, and one (2.5%) had an undifferentiated tumor. Twenty-six patients had Barrett's mucosa. Before treatment, the patients' tumors were staged as follows: 12 were T2N0, three were T2N1, 16 were T3N0, eight were T3N1, and one was T4N0. Thus 28 of 40 patients (70%) had locally advanced esophageal cancer (T3, or stage IIB or greater).

The induction program was rigorous and relatively toxic. Most patients required nutritional support to complete this protocol. The average length of stay related to the induction treatment was 17 (8 to 50) days. A 10-day period was required for completion of

both cycles of chemotherapy, so on average 7 additional hospital days were required to deal with side effects or complications of therapy. The complications of chemotherapy according to the dose of paclitaxel are listed in Table I. A dose of 100 mg/m² was chosen to continue the phase II study on the basis of acceptable levels of toxicity. Other complications of induction treatment included pneumonia (four cases), anaphylactic reaction to paclitaxel (two cases), myocardial infarction (two cases), line sepsis (two cases), subclavian vein thrombosis (two cases), pericarditis (one case), empyema (one case), stroke (one case), and toxic colitis (one case). Four patients were no longer eligible for operation as a result of toxicity in three cases and disease progression (liver metastasis) in the other. Two patients died during induction therapy, one of severe pneumonia and the other of myocardial infarction. Thirteen of 40 patients (33%) required chemotherapy dose reduction. Nine patients had dose reductions, in response to esophagitis in five cases and hematologic toxicity in four. Four patients had only one cycle of chemotherapy because of pneumonia in one case, toxic colitis in one, paclitaxel anaphylactic reaction in one, and a myocardial infarction in the fourth. All patients completed radiation therapy.

Thirty-six patients (90%) underwent resection an average of 77 days after the initiation of treatment. Twenty patients had a left thoracoabdominal approach, 14 had an Ivor Lewis approach, and two underwent transhiatal esophagectomy. Complications developed in six patients (17%): chylothorax in

Fig. 2. Kaplan-Meier survival curve for all 40 patients registered in the study.

one, adult respiratory distress syndrome in two, aorto-gastric fistula in one, stomach necrosis in one, delirium in one, and respiratory failure in one. Both patients with adult respiratory distress syndrome died, one of multiorgan failure and one of an aortogastric fistula. The average length of stay after esophagectomy was 22 (range 7 to 72, median 10) days. Total treatment-related mortality was 10% (4/40).

Fourteen of 36 patients had no tumor present in the resected specimen, for a pathologic complete response rate of 39%. Fifteen of 36 patients (42%) had no tumor in the resected esophagus. Twenty-four of 36 patients (67%) had no tumor in the resected lymph nodes. The postsurgical staging was as follows: T0N0, 14; T0N1, one; T1N0, four; T1N1, one; T2N0, three; T2N1, four; T3N0, three; and T3N1, six. Twenty-four of 36 patients (67%) were in lower stages than before treatment. The pathologic complete response rates were 33%, 50%, and 38% at paclitaxel doses of 75, 125, and 100 mg/m², respectively. Patients who were able to tolerate the complete chemotherapy regimen had a higher complete response rate than did those who required dose reduction ($p = 0.076$; Table II). There was a trend ($p = 0.18$) toward a higher pathologic complete response rate among patients who had squamous cell carcinoma than among those who had adenocarcinoma (Table III). All the patients with squamous cell cancer had locally advanced disease (T3 or stage IIB or greater), and four of six required chemotherapy dose reduction. Accordingly, the prognostic variables of stage and chemotherapy completion did not explain the trend toward an

Table IV. Survival and complete response rates with induction chemoradiotherapy for esophageal cancer

First author	Year	No. of patients	PCR (%)	Treatment-related mortality (%)	%	
					1 yr	2 yr
Walsh ²	1996	58	25	9	52	37
Forastiere ³	1993	43	24	7	70	61
Wright (current report)	1997	40	39	10	81	61

PCR, Pathologic complete response rate.

increased response rate among patients with squamous cell cancer.

Nine patients died during this study: four of treatment complications, three of progression of disease (liver metastases in three, peritoneum in one, and low periaortic nodes in one), one of respiratory failure more than a year after treatment, and one of a late myocardial infarction. Of the three patients who died of esophageal cancer after treatment, one had disease progression during induction treatment (liver and peritoneum), one had a pathologic complete response (T3N1 to T0N0), and one had an incomplete response (T3N1 to T0N1). A preliminary Kaplan-Meier survival curve is depicted in Fig. 2. The 1-year survival rate was 81% (95% CI 68% to 95%), and the 2-year survival rate was 61% (95% CI 35% to 86%). The median follow-up is 11.9 months. The mean cost of treatment per patient was \$50,209 dollars (\$31,446 to \$109,621). The mean hospital cost related to induction chemotherapy and radiotherapy was \$23,091 dollars (\$14,810 to \$52,487). The mean hospital cost for esophagectomy was \$24,989 (\$15,338 to \$85,639).

Discussion

This phase I and II trial of induction chemoradiotherapy demonstrated that the maximum tolerated dose of paclitaxel was 100 mg/m². This was an intense regimen, though, with some toxicity developing in most patients. Esophagitis necessitating nutritional support was the most common toxic effect, occurring in all patients at 125 mg/m² paclitaxel and in 57% of patients at 100 mg/m². Hematologic toxicity was uncommon. Pneumonia developed in four patients, probably as a result of dysphagia-induced microaspiration and depressed immunity from chemoradiotherapy. Adult respiratory distress syndrome occurred in two patients after esophagectomy, which has been rare in our experi-

ence in patients treated with resection alone or with chemotherapy followed by resection. Myocardial infarction developed in four patients, in two during induction treatment and in two after completion of all treatment. These patients had a history of stable coronary disease, but the issue of possible initiation of an unstable pattern by induction chemoradiotherapy must be raised.⁸ The total treatment-related mortality rate was 10%, which is similar to other reports of induction chemoradiotherapy but higher than among patients who undergo resection only.^{2,3,9} The decline in quality of life, length of hospital stay (average 17 days), and cost during induction therapy are significant and must be weighed against possible enhanced long-term survival. Although our median length of stay after esophagectomy was only 10 days, our mean stay was 22 days, reflecting several outliers with severe complications. This increased length of stay reflects the toxicity of this program and is in contradistinction to our previous reports, in which the addition of chemotherapy alone did not affect length of stay.⁹ Only the significant prolongation of survival will make these costs worth bearing.

This trial of an intensive induction program with paclitaxel and high-dose hyperfractionated radiotherapy resulted in a high (39%) complete response rate. Response rates were higher among patients with squamous cell carcinoma and patients who had the complete course of chemotherapy, as has been reported before.^{2,3,7} The three deaths of recurrent disease were all related to distant metastases, suggesting good local control with this regimen. Although the follow-up period has been short, the 2-year survival rate of 61% (95% CI 35% to 86%) is encouraging. Obviously, additional observation will be required to determine whether patients are cured or the appearance of metastases has just been delayed. The entry criteria were meant to be relatively inclusive, to allow treatment of the broad spectrum of patients with esophageal cancer who so often have comorbid disease. The patients in this study are typical of modern North American series: 80% of patients with adenocarcinomas, 65% with Barrett's mucosa, and 70% with locally advanced tumors. The toxicity incurred in achieving these results is substantial and will only bear scrutiny if marked prolongation of survival occurs.

The high (39%) pathologic complete response rate achieved compares favorably with other reports (Table IV). Our data are preliminary, and further follow-up will be necessary to see whether the

remissions are durable. This regimen is too toxic for the majority of patients and should not be generalized for application to most. Stricter entrance criteria for age, performance status, pulmonary disease, and cardiac disease would likely lead to less toxicity. It is also likely that starting enteral nutritional support before therapy would be of benefit. The relatively large dose of radiation for an induction program (58.5 Gy to the tumor and 45 Gy to the mediastinum, where the esophageal anastomosis is made) probably contributed to the complications and will have to be reduced. The relative influence of chemotherapy versus radiotherapy on the complete response rate is unknown. Local control has been excellent with induction chemoradiotherapy, and distant metastasis has been the primary reason for relapse. More efficacious systemic therapies (e.g., with paclitaxel), rather than more intense radiotherapy strategies, should therefore be pursued. We plan to investigate another regimen with the same dose of paclitaxel (100 mg/m²), a reduced dose of 5-fluorouracil, carboplatin, and a reduced amount of radiotherapy (40 Gy).

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Discussion

Dr. Michael E. Burt (*New York, N.Y.*). I congratulate you for carrying out a well-designed and implemented phase I and II trial of intensive induction chemoradiotherapy in esophageal carcinoma. As presented, this was an extremely intensive regimen, with subsequent high morbidity and an increased mortality rate. More than 50% of the patients had severe esophagitis, and other morbidities occurred in 40%. This led to a chemotherapy dose reduction in 33% of the patients, with subsequent decreased tumor response and delays in the planned operation. Despite the high morbidity of this induction regimen, however, 39% of the resected patients had a complete pathologic response. This is slightly higher than the 28% response reported by Dr. Orringer's group and the 25% reported by Dr. Walsh's group.

I have three interrelated questions. Because chemotherapy and radiation therapy alone in randomized trials have been reported to carry a 25% 5-year survival rate, and your trial reported a 39% complete response to induction chemoradiotherapy, what do you consider the role of surgery to be in localized esophageal carcinoma after chemotherapy and radiation therapy? Also, in future trials are you looking at the role of newer modalities, such as positron emission tomographic scanning, to predict a complete response? And what is the role of surgery for those patients?

Dr. Carolyn E. Reed (*Charleston, S.C.*). At the Medical University of South Carolina, we have used two cycles of paclitaxel (Taxol), cisplatin, and 5-fluorouracil alone as induction therapy in 20 patients, all in stage III. Our Taxol dose was 250 mg/m². Our pathologic complete response rate was 15%. Clearly, radiation therapy is adding significantly to the pathologic complete response rate, as has been shown in other phase II and III studies. However, other studies have shown that adding radiation therapy to a three-drug regimen substantially increases morbidity.

I have two questions. First, why did you choose hyperfractionated radiotherapy, which in a rural setting is either not feasible or extremely expensive? Second, was pulmonary toxicity a concern, and is that one of the reasons you used a lower Taxol dose? Would you consider using two drugs with radiation therapy in a multiinstitutional setting? If so, which two drugs?

Dr. Nasser K. Altorki (*New York, N.Y.*). I congratulate you on undertaking a fairly brave regimen before esoph-

ageal resection and yet accomplishing it with the usually excellent results that we are accustomed to from the Massachusetts General group. Some of my concerns have been already echoed by Dr. Reed. You noted in your presentation that the esophagus was quite edematous at the time of the operation. Would you comment on whether that has affected the anastomotic complication rate, which is usually exceedingly low from the Massachusetts General Hospital?

Dr. Wright. To address Dr. Burt first, with respect to the role of surgery after induction treatment, previous reports from our hospital indicate that even with endoscopic ultrasonography we have unable to predict a complete response after induction chemotherapy or chemoradiotherapy. Accordingly, surgery still has a role in these cases. Indeed, despite this intense regimen, 60% of patients had residual disease that was resected. Whether there will be long-term survivors among those who have resected residual disease remains to be seen, but Forastier's data from Michigan do indicate that patients undergoing resection of persistent disease do have a meaningful five-year survival. We have investigated positron emission tomographic scanning in lung cancer, especially in patients with N2 disease who undergo induction chemoradiotherapy, but we have not yet begun this in esophageal cancer.

To address Dr. Reed's questions, why hyperfractionated radiotherapy twice daily? In part it was because our radiation therapist, Dr. Choi, has had a long-standing interest in pursuing this avenue. We realize it is not available in most hospitals, but we wanted to create a program that was maximally intense and see what we could achieve. Obviously, to some extent we paid the price for that. I do think that some of our pulmonary toxicity was caused by the radiation, and the radiation dose needs to be significantly reduced.

I think we are still going to be firmly committed to three drugs, but with a much smaller dose of radiation therapy to allow us to give the drugs in larger doses. This should control distant micrometastatic disease.

Last, regarding our anastomotic complication rate, we had one late fistula after a patient was on a ventilator for a month with adult respiratory distress syndrome. This fistula subsequently eroded into the aorta, so we had an anastomotic complication rate of 2.5%, which is acceptable for such an intense induction program.