Phase 2: a dose-escalation study of OncoGel (ReGel/paclitaxel), a controlled-release formulation of paclitaxel, as adjunctive local therapy to external-beam radiation in patients with inoperable esophageal cancer

G. Aaron DuVall[a], Dino Tarabar[c], Richard H. Seidel[a], Nancy L. Elstad[b] and Kirk D. Fowers[b]

OncoGel, a novel injectable formulation of paclitaxel in a biocompatible biodegradable gel (ReGel), provides controlled release of paclitaxel at the injection site, resulting in high intralesional paclitaxel concentrations and continuous radiosensitization without attendant systemic toxicities. This dose-escalation study evaluated the toxicity, pharmacokinetics, and preliminary antitumor activity of OncoGel injected intralesionally in patients with inoperable esophageal cancer who were candidates for palliative external-beam radiotherapy (RT). Eleven patients with inoperable advanced esophageal cancer received a single administration of OncoGel into the primary tumor using conventional endoscopic techniques. Three cohorts received approximately one-third of the tumor volume with increasing paclitaxel concentrations to achieve 0.48, 1.0, and 2.0 mg paclitaxel/cm^3 tumor volume. Subsequent to injection, RT was initiated (50.4 Gy in 1.8 Gy fractions). Pharmacokinetic sampling was performed. All patients completed the study. No dose-limiting toxicities were reported. Dysphagia improved and tumor size decreased in most patients. Biopsies were negative for carcinoma in 4 of 11 patients. Peak paclitaxel plasma concentrations were low (0.53–2.73 ng/ml) and directly related to the absolute amount of paclitaxel administered. Paclitaxel was detectable in plasma for 24 h in all patients and for 3 weeks in six patients. OncoGel given as an adjunct to RT was well tolerated in patients with inoperable esophageal cancer and provided prolonged paclitaxel release with minimal systemic exposure. OncoGel plus RT seemed to reduce tumor burden as evidenced by dysphagia improvement, tumor size reduction, and negative esophageal biopsies. The addition of OncoGel to combined modality therapy merits continued clinical development. ***Anti-Cancer Drugs*** **20:89–95 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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[a]Digestive Health Specialists of Tyler, Tyler, Texas, [b]Protherics Salt Lake City Inc., a BTG plc Company, Utah, USA and [c]Gastroenterology Clinic, Military Medical Academy, Belgrade, Serbia

Correspondence to Dr Kirk D. Fowers, PhD, Protherics Salt Lake City, Inc., 2417 South 3850 West, Suite 150, West Valley City, UT 84120, USA
Tel: +1 801 433 2560; fax: +1 801 433 2561; e-mail: kirk.fowers@btgplc.com

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Introduction

Esophageal cancer causes 300 000 new deaths per year worldwide [1]. Disease stage is highly predictive for survival; 80% of individuals with local disease superficial to the esophageal musculature (pathologic stage I) survive up to 5 years [2]. Local and locoregionally advanced diseases (pathologic stages II and III) are associated with 5-year survival rates of 34 and 15% of patients, respectively. Patients with stage IV (metastatic) disease cannot be cured with current therapies and have a median survival of about 6 months [3–5]. Unfortunately, esophageal cancer tends to be symptomatic only when the disease is relatively advanced. Thus, a small minority of patients (approximately 10%) have stage I disease at the time of diagnosis, whereas as many as 50% of patients present with stage IV disease [6]. Patients with stage II or III disease (approximately 30–40% of patients) represent a substantial population for which cure or long-term survival is possible and for whom current therapy offers suboptimal results. New therapeutic modalities that improve local response with limited toxic potential may result in increased survival for these patients.

OncoGel (Protherics Salt Lake City, Inc., a BTG plc Company, Utah, USA) is paclitaxel formulated in a thermosensitive biodegradable polymer, ReGel (Protherics), which is liquid at room temperature but forms a gel at body temperature. OncoGel was designed to allow controlled release of paclitaxel over 6 weeks at the injection site and to provide a high local concentration without significant systemic exposure and its attendant systemic toxicity. In a phase 1 study, OncoGel was well tolerated, remained localized at the injection site and did not reach the systemic circulation in clinically significant amounts [7]. A maximum tolerated dose (MTD) was not identified as dose-limiting toxicities

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(DLTs) were not encountered. In addition, there were preliminary indications that OncoGel reduced tumor size.

OncoGel provides a high intralesional concentration of paclitaxel with negligible systemic exposure. It has limited potential to produce systemic toxicity and thus may offer the possibility of optimizing treatment response in patients with esophageal cancer without increasing the complications of significant treatment-related morbidity associated with concurrent therapy [i.e. chemotherapy, external-beam radiotherapy (RT), surgery]. Paclitaxel is known to be active against both squamous and adenocarcinoma of the esophagus [4] and to be a potent radiosensitizer [8,9]. This study combined OncoGel injection into esophageal primary tumors and selected adjacent involved regional lymph nodes with RT in patients with advanced disease to determine the safety and tolerability of this dual therapy regimen and assess its activity.

Patients and methods

Eligibility

Surgically or medically inoperable patients with histologically or cytologically confirmed adenocarcinoma or squamous cell carcinoma of the esophagus who were candidates for palliative RT were enrolled. Patients with tumors having the following characteristics were excluded from the study: vascular invasion or involvement; tracheoesophageal fistulas; invasion into the tracheal mucosa or major bronchus; and/or extension beyond 2 cm into the stomach. Patients who had previously received photodynamic therapy, esophageal stent placement, or RT to the esophagus were also excluded.

At screening, patients were required to have symptoms of dysphagia (grade 3, 4, or 5, Table 1), Karnofsky Performance Status (KPS) of at least 60, and a minimum life expectancy of 4 months. Females were required to be nonpregnant and nonlactating. Adequate hematapoetic, hepatic, and renal functions were required. Patients with medical histories of significant severe or uncontrolled cardiovascular disease, respiratory disease, neurological disease, or active infections were excluded. A history of a prior malignancy was allowed, provided that more than 2 years had elapsed since diagnosis with no current evidence of active disease; patients with nonmelanoma skin cancer or carcinoma *in situ* of the cervix, uterus or breast in the previous 2 years were eligible for study entry. Chemotherapeutic agents, vaccines, or biological response modifiers/growth factors were not permitted within 4 weeks of enrolment.

Table 1 Dysphagia assessment

Grade	
1	Asymptomatic
2	Difficulty swallowing some solid foods but ability to swallow semisolid foods
3	Difficulty swallowing solids but ability to swallow liquids
4	Difficulty swallowing liquids
5	Inability to swallow anything, including saliva

Pretreatment and follow-up evaluations

Local ethics committee's approval of the study was required and all patients provided informed consent before enrolment. Before study entry, esophageal tumor evaluation, biopsy and staging using standard of care endoscopic ultrasound (EUS) or computed tomography scan procedure was carried out. Surgical ineligibility was documented. Medical histories, physical examinations, laboratory assessment of hematopoietic, hepatic, and renal functions, KPS determination, [10] and dysphagia assessment [11] (Table 1) were carried out before OncoGel administration, and every 2–3 weeks for 11 weeks.

Protocol-specified endoscopies were carried out at baseline and week 11 to measure tumor volume and for visual assessment of esophageal and tumor appearance. Esophageal biopsies were carried out at week 11. In addition, at week 11 investigators assessed whether or not the patient might be considered a candidate for esophageal resection. This assessment only considered the condition of the esophagus; any other comorbid or health conditions were not taken into consideration for this evaluation.

Dose and drug administration

OncoGel was supplied by Protherics in ready-to-use single-use prefilled glass syringes and packaged as bulk supplies. Syringes were stored at $-20^{\circ}C$ ($\pm 5^{\circ}C$) and thawed at room temperature for at least 1 h before injection. OncoGel was transferred to a screw syringe for delivery using a 19-gauge endoscopic needle.

A single dose of OncoGel was administered using linear EUS guidance using standard conscious sedation techniques. Three cohorts were administered OncoGel containing paclitaxel concentrations of 1.5, 3.1 or 6.3 mg paclitaxel/ml of OncoGel. An amount of OncoGel that was approximately one-third of the total tumor volume (as measured by radial EUS at screening) was administered using multiple injections of 0.25–1.0 ml aliquots into the primary tumor to attain a final tumor concentration of 0.48, 1.0, or 2.0 mg paclitaxel/cm^3 tumor volume (Table 2). OncoGel was also administered to endoscopically accessible involved lymph nodes (per investigator discretion) at approximately one-third of the node's volume.

RT began within 3 days after OncoGel administration, with 50.4 Gy administered in 28 fractions of 1.8 Gy. The following recommendations regarding treatment fields and techniques were provided to the clinical sites. The initial target volume was to include a 5 cm proximal and distal margin and a 2–3 cm radial margin. Supraclavicular

Table 2 Dose-escalation scheme

Dose level	No. of patients/cohort	Dose escalation	OncoGel concentration (mg/ml)	Tumor volume injected (%)	Paclitaxel concentration in tumor (mg/cm^3)	Daily dose of RT (Gy)
1	3–5	Starting dose	1.5	33	0.48	1.8
2	3–5	2 × level 1	3.1	33	1.0	1.8
3	3–5	2 × level 2	6.3	33	2.0	1.8

RT, radiotherapy.

or celiac nodes were to be included in the target volume, as appropriate. The dose to the initial target volume, calculated at isocenter, was to be 45 Gy in 25 fractions of 1.8 Gy. The final 5.4 Gy was to be given as a boost to a reduced volume (3 cm proximal and distal margins) in three fractions of 1.8 Gy.

Adverse events (AEs) were graded according to the National Cancer Institute Common Toxicity Criteria v 3.0, 2003 (*http://ctep.cancer.gov/forms/CTCAEv3.pdf*) [12]. Adverse event data were collected for all treatment-emergent AEs, regardless of potential attribution to OncoGel. Each event was evaluated for its relationship with OncoGel administration and/or RT.

Dose-escalation design

The dose-escalation scheme was planned to enrol a minimum of three patients per cohort; one additional patient could be enrolled per cohort even in the absence of DLTs to allow for patient dropout. Once three to four patients were enrolled into a cohort, study enrolment was closed until after the final patient completed the week 8 visit and safety data were reviewed for the occurrence of protocol-defined DLTs (Table 3). If a DLT occurred in the first three or four patients, additional patients would be enrolled until five patients completed through the 8-week DLT assessment period. The medical monitor reviewed all safety data for a completed cohort before authorizing enrolment of patients at the next dose level.

Identification of the MTD was to be based on the occurrence of DLTs in the study. The MTD would be exceeded if at least two of five (40%) patients experienced the same DLT at a dose level.

Plasma sampling and assay

Plasma samples for pharmacokinetic analysis were collected before intralesional injection, at 3, 6, 24, and 72-h postdose, and at week 3. Paclitaxel concentrations were determined using a validated high-performance liquid chromatography tandem mass spectrometer assay (paclitaxel human validation: report for LC/MS/MS validation of paclitaxel, 3-*p*-hydroxy paclitaxel, and 6α-hydroxy paclitaxel in human plasma 2000; BASi Northwest Labs Inc., McMinnville, Oregon, USA).

Table 3 Local and systemic dose-limiting toxicities definitions

Local dose-limiting toxicities	
≥ Grade 4	Hemorrhage or bleeding of the esophagus
≥ Grade 4	Perforation of the esophagus not as a result of EUS and/or dilation before drug administration
≥ Grade 4	Necrosis of the esophagus
Systemic dose-limiting toxicities	
≥ Grade 4	Neutropenia lasting >5 days
≥ Grade 4	Febrile neutropenia regardless of duration
≥ Grade 4	Thrombocytopenia

EUS, endoscopic ultrasound.

Table 4 Tumor response from measurements taken during radial EUS

Response	Cross-sectional area	RECIST (longest diameter)[a]
Progressive disease	>44% Increase	>20% Increase
Stable disease	<50% Decrease and ≤ 44% increase	<30% Decrease and ≤ 20% increase
Partial response	≥ 50% Decrease	≥ 30% Decrease
Complete response	Disappearance	Disappearance
Total shrinkage or response	Disappearance or no increase	Disappearance or no increase

EUS, endoscopic ultrasound, RECIST, Response Evaluation Criteria in Solid Tumors.
[a]RECIST guidelines for evaluating the longest diameter were modified in that only the primary tumor was included in the measurements and there was a single assessment at week 11 (rather than repeat assessments separated by at least 4 weeks to verify response); however, response criteria for the percentage change in longest diameter are the same as those presented by Therasse [13].

Endpoints

The primary safety endpoint was identification of the MTD of OncoGel when administered concurrently with RT. The primary efficacy endpoint was the attainment of a 2-category or greater decrease in dysphagia grade from baseline to week 11. Tumor response from baseline to week 11 was also evaluated. Changes in primary tumor size were evaluated from measurements taken during radial EUS at baseline and week 11 to determine complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) (as defined in Table 4; [13]) from both the largest cross-sectional area and modified Response Evaluation Criteria in Solid Tumors (RECIST) (longest diameter). Tumor volume was calculated from the cross-sectional area and diameter measurements. Other endpoints were esophageal biopsy, resectability, KPS, and clinical laboratory assessments.

Statistical methods

This study was conducted using a modified dose-escalation study design, such that three to five patients per cohort would be enrolled for a total of nine to 15 patients. Two data analysis sets, the intention-to-treat (ITT) and per-protocol (PP) populations, were predefined. The ITT population comprised of patients who received study drug and the PP population comprised of patients in the ITT population who had no significant protocol deviations. Continuous variables were summarized using descriptive statistics (number of patients, mean, standard deviation, minimum, and maximum). Frequencies and percentages for each category were used to summarize categorical variables. Descriptive statistics were presented by cohort and visit. On account of small sample sizes, no inferential statistical analyses were planned or conducted.

Noncompartmental pharmacokinetic analysis was conducted for the ITT population. Descriptive statistics were presented by cohort and time point for plasma concentration levels of paclitaxel and by cohort for pharmacokinetic parameters.

Results

Patients

Between September 2005 and March 2007, 11 patients participated in the study and received OncoGel. Patients were enrolled at two centers: seven patients in the United States and four patients in Serbia. One additional patient (cohort 3) was a 'screen failure' because the investigator was unable to pass the EUS probe through the lumen on dosing day due to the presence of exophytic tumor, precluding OncoGel injection. Patient and tumor baseline characteristics are presented in Table 5.

Table 5 Patient and tumor characteristics

Patient demographics	No.	%
Sex		
Female	2	18
Male	9	82
Age (years)		
Mean	66	
Range	53–79	
Race		
Black	1	9
White	10	91
Dysphagia grade		
3	10	91
4	1	9
Stage at diagnosis		
III	8	73
IV	3	27
Karnofsky Performance Status		
90	3	27
80	7	64
50[a]	1	9
Tumor type		
Adenocarcinoma	6	55
Squamous cell	5	45
Tumor morphology		
Exophytic	8	73
Intrinsic	3	27
Tumor location		
Middle thorax	2	18
Upper thorax	9	82
Tumor measurements (radial EUS)	Range	
Volume (cm^3)	6.14–111.60	
Area (cm^2)	2.05–14.80	
Longest diameter (cm)	0.90–4.25	
Length (cm)	3–9	

EUS, endoscopic ultrasound.
[a]KPS of 50 because of previous cerebrovascular accident.

All patients were assessable for DLTs and completed all 11 weeks of the study. There were no significant protocol deviations, therefore the ITT and PP populations were identical.

Doses administered

The tumor volumes at baseline ranged from 6 to 112 cm^3. All patients received a single administration of OncoGel ranging from 28 to 41% of the estimated tumor volume, closely approximating the protocol-specified one-third tumor volume as determined by radial EUS. In addition, four patients had involved lymph nodes injected with OncoGel. The total volume of OncoGel administered to both tumor and involved lymph nodes ranged from 3 to 36 ml, delivered in 4 to 53 aliquots. The total amount of paclitaxel administered to patients ranged from 16.2 to 188 mg as presented in Table 6. All patients received the protocol-specified RT dose of 50.4 Gy delivered in 28 fractions.

Dose-limiting toxicity assessment

No protocol-defined DLTs were reported in the study. Severe AEs not considered to be DLTs included metabolism/nutrition, musculoskeletal, gastrointestinal, respiratory, nervous system and cardiac disorders, or neoplasms/disease progression. These grade 3/4 AEs, regardless of relationship to treatment, are presented in Table 7.

Fourteen events, occurring among five patients, were considered by the investigators to be at least remotely related to OncoGel administration. Sixteen AEs occurring among six patients were considered to be related to RT alone. Of these events, 11 occurring among four patients were considered to be at least remotely related to the combination of OncoGel and RT. These events are presented in Table 8.

Dysphagia

Dysphagia improved from baseline (dosing day 1) through study week 11 for nine (82%) patients, with a two-point improvement reported for six (55%) patients and one-point improvement for three (27%) patients. Changes in dysphagia scores over time are displayed in Fig. 1.

Tumor response

Tumor response by EUS determined cross-sectional area was PR for two patients, SD for six patients, and PD for two patients. Tumor measurements were not obtained for one patient at week 11 because of the inability to pass the

Table 6 Amount of paclitaxel administered

	Dose level (mg paclitaxel/cm^3 tumor volume)		
	Cohort 1 0.48	Cohort 2 1.0	Cohort 3 2.0
Total number of patients (*n*)	3	4	4
Size of primary tumor (cm^3)			
Mean	68.59	31.79	37.58
Range	27.9–111.6	19.0–63.0	6.1–88.8
Volume (ml) of OncoGel injected			
Mean	22.40	10.68	12.68
Range	10.80–36.00	6.40–21.20	2.50–29.80
% Tumor volume injected			
Mean	33.91	33.54	34.21
Range	30.80–38.67	33.23–33.76	28.17–40.69
Amount (mg) of paclitaxel injected into primary tumor			
Mean	33.60	33.09	79.85
Range	16.20–54.00	19.84–65.72	15.75–187.74
Amount (mg) of paclitaxel injected into lymph nodes			
N	2	1	1
Mean	1.31	3.10	11.97
Range	0.38–2.25	3.10	11.97
Total amount (mg) of paclitaxel per patient (tumor + lymph node)			
Mean	34.48	33.87	82.85
Range	16.20–54.38	20.15–65.72	18.90–187.74
Total number of injections per tumor			
1–10	0	1	2
11–20	1	1	1
21–30	0	2	0
31–40	1	0	1
41–50	0	0	0
51–60	1	0	0
Gy delivered	50.4	50.4	50.4

Table 7 Grade 3 and 4 non-DLT adverse events (*N*=11)

	Dose level (mg paclitaxel/cm^3 tumor volume)		
	Cohort 1 0.48	Cohort 2 1.0	Cohort 3 2.0
Number of patients per cohort (*n*)	3	4	4
Grade 3 (severe)			
Abdominal pain, upper	1	0	0
Anorexia	1	1	0
Aspiration	1	0	0
Bradycardia	0	0	1
Dehydration	0	1	0
Musculoskeletal pain	0	1	0
Neck pain	0	1	0
Syncope	1	0	0
Vomiting	0	0	1
Grade 4 (life-threatening)			
Malignant neoplasm progression	1	0	0
Metastatic neoplasm	0	1	0

DLT, dose-limiting toxicity.

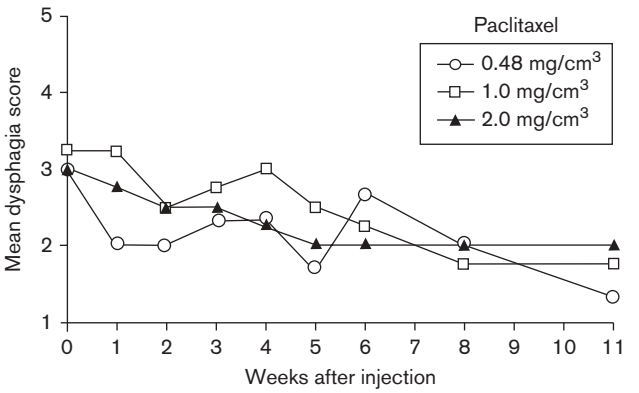
EUS probe through the lumen. Using modified RECIST, five patients were classified as having PR and five as having SD, with no patients considered to have PD.

Table 8 Adverse events related to OncoGel, RT, or OncoGel and RT

	Related to OncoGel	Related to RT	Related to OncoGel and RT[a]
Total patients reporting related adverse events (*n*)	5	6	4
Adverse events			
Anorexia	3	4	3
Dysgeusia	2	2	2
Nausea	2	3	2
Oesophageal pain	2	0	0
Abdominal pain upper	1	1	1
Dry mouth	1	1	1
Fatigue	1	2	1
Pyrexia	1	0	0
Weight decreased	1	2	1
Radiation oesophagitis	0	1	0
Stomatitis	0	1	0

RT, radiotherapy.
[a]Includes events considered related to both OncoGel and RT for the same patient. These events are also included in the 'Related to OncoGel' and 'Related to RT' columns so do not represent additional events to those in the aforementioned columns of the table.

Fig. 1



Mean dysphagia scores versus time by dose cohort.

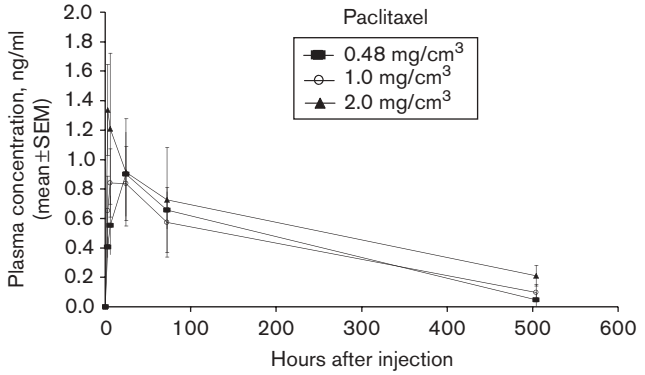
Esophageal biopsies and resectability

Biopsies at week 11 were negative for carcinoma for four of 11 patients, whereas carcinoma was present for six patients and data were not available for one patient in cohort 2. Two patients with stage III disease and PR by modified RECIST were considered resectable at week 11 by the investigator and were thus scheduled for surgery. Only one of these patients was, however, resected; the other was later deemed unsuitable for resection because of a new diagnosis of a second primary tumor (rectal cancer).

Pharmacokinetics

Paclitaxel was detectable in plasma for 24 h in all 11 patients, for 72 h in 10 patients, and for 3 weeks in six patients. Mean paclitaxel levels versus time are presented by dose cohort in Fig. 2. Peak paclitaxel plasma concentrations (C_{max}) ranged from 0.53 to 2.73 ng/ml

Fig. 2



Mean plasma paclitaxel concentration (nanogram/milliliter) versus time.

(limit of quantification = 0.10 ng/ml). Peak plasma concentrations were directly related to the absolute amount of paclitaxel administered. T_{max} (the time of occurence of C_{max} ranged from 3 to 24 h.

Conclusion

Local OncoGel injection to primary esophageal tumor, and in some instances to regional involved lymph nodes, was well tolerated with no treatment-limiting toxicities. The MTD was not identified at the highest concentration of OncoGel administered in the study. Pharmacokinetic data showed prolonged release of paclitaxel from OncoGel, but only minimal systemic exposure and no dose-limiting systemic toxicities (as evidenced by no AEs reported associated with hematologic laboratory parameters), at the doses studied.

Patients enrolled on this study had advanced disease, were considered to be inoperable at the time of enrolment and were being treated with palliative intent. Six of 11 (55%) patients met the efficacy endpoint of a two-point decrease in dysphagia. A palliative benefit as evidenced by at least a one-point decrease in dysphagia score was experienced by nine of 11 (83%) patients. Although these findings must be qualified in view of the absence of a concurrent control and the limited sample size, the frequency of palliative benefit observed in this study seems to be as great as or greater than palliation rates reported in the literature. Literature reports on the effect of RT on dysphagia describe rates of palliation ranging from approximately 60 to 85% [14].

An unexpected finding on this study was the observation of negative esophageal biopsies in four of 11 patients (36%). Reports of the frequency of negative biopsy findings after RT alone are difficult to obtain. Persistent or recurrent primary tumor is a common cause of treatment failure in esophageal cancer both in patients treated with RT alone and in those treated with chemoradiotherapy, with and without subsequent surgery [14]. Petrovich *et al.* [15] reported histologically confirmed CR in 16 of 137 (12%) patients treated with external-beam RT alone. Herskovic *et al.* [16] reported that two of 13 (15%) biopsies were negative for carcinoma in a small subset of patients receiving 64 Gy, 32-fraction RT in a comparative study of RT versus chemoradiotherapy. To what extent these observations can be extrapolated to the patients treated on this study is unknown.

The absence of tumor in surgical specimens (i.e. pathologic CR) and the presence of tumor-free resection margins in patients with esophageal cancer correlate highly with long-term survival [17,18]. This finding of negative esophageal biopsies in a relatively high proportion of patients on this study suggests that the addition of OncoGel to currently used combined modality therapy could favorably impact pathologic CR rate and tumor-free margin frequency, and consequently the long-term survival and the potential for cure for patients with stage II and III diseases. Therefore, further study of OncoGel in a combined modality setting is warranted.

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