

The Evolving Treatment of Anal Cancer

How Are We Doing?

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Hypothesis: The adaptation of new techniques in treatment of epidermoid carcinoma of the anal canal during the past 3 decades has improved clinical outcomes.

Design: Retrospective consecutive case review.

Setting: A university hospital and Veterans Affairs medical center.

Patients: Medical records of 76 consecutive patients treated for invasive epidermoid cancer of the anal canal between 1970 and 1999 were reviewed. Twenty-one patients were excluded because of inadequate staging information and/or follow-up of less than 12 months.

Main Outcome Measures: Locoregional recurrence, survival, colostomy-free survival, and morbidity.

Results: Fifty-five patients composed the study population. Ten were treated during decade 1 (1970-1979), 16

in decade 2 (1980-1989), and 29 in decade 3 (1990-1999). Mean age and sex distributions were similar. The prevailing primary treatment modality changed during the course of the study from sequential treatment (chemotherapy then radiation therapy then radical surgery) to concurrent chemoradiation (70% and 0% of cases, respectively, in decade 1 to 7% and 76% of cases, respectively, in decade 3). Locoregional control (50%, 81%, and 93%; $P=.01$), crude survival (median, 28, 30, and 76 months), and colostomy-free survival (mean, 13, 90, and 80 months) improved during the 3 decades. There were no differences in major complications during the 3 decades (40%, 56%, and 41%).

Conclusion: Primary treatment with concurrent chemoradiation has improved the local recurrence, survival, and colostomy-free survival rates in patients with invasive epidermoid carcinoma of the anal canal without increasing major morbidity.

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ANAL CANAL cancer is rare and only accounts for 1% to 6% of all anorectal neoplasms.¹ It is important to distinguish anal canal from anal margin neoplasms, as the former are much more aggressive and therefore treated as such. The anatomic landmarks of the anal canal are the anorectal ring proximally and the anal verge distally.² The anal margin is defined as the perianal skin extending 5 cm out from the anal verge. Most anal canal tumors (squamous, cloacogenic, basaloid, and transitional) behave in similar fashions and are collectively termed *epidermoid carcinomas*.

The goals in the treatment of epidermoid cancer of the anal canal are cure, local control, sphincter salvage, and avoidance of a permanent colostomy, all the while attempting to minimize morbidity. Great strides have been attained during the past 3 decades toward achieving these goals. Through the 1970s, abdominoperi-

neal resection was the standard treatment for anal canal cancer. The resulting permanent colostomy, high local recurrence rates, and 5-year survival rates of only 37% to 71%³ inspired researchers to seek alternative methods of treatment. Extrapolating from encouraging results of combined chemotherapy and radiation in the treatment of advanced stomach cancers, Nigro et al⁴ reported the first successful use of combined fluorouracil and mitomycin with 3000 rad (30 Gy) of concurrent external beam radiation as a potentially curative modality for advanced anal cancer. While this combined chemoradiation was initially used to downstage tumors before radical resection, surgery was eventually omitted in cases where clinical complete response to chemoradiation was found.⁵

During the subsequent 15 years, the various roles of the chemotherapy and radiation therapy have been clarified in cooperative group randomized trials in the

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PATIENTS AND METHODS

A search of the medical record databases and tumor registries at Oregon Health Sciences University, Portland, and the Portland Veterans Affairs Medical Center identified 76 patients treated for invasive epidermoid carcinoma of the anal canal during the 3 decades spanning 1970 to 1999. Their medical records were reviewed. All patients had biopsy-proved invasive primary epidermoid (squamous, cloacogenic, basaloïd, or transitional cell) carcinoma of the anal canal and underwent definitive treatment at our institutions. Anal margin, gynecologic, nonepidermoid, and in situ neoplasms were not included in this study. Tumor staging information was extracted from the medical record and translated into 1998 American Joint Committee on Cancer format² in an effort to make comparisons across time. Twenty-one patients were excluded from final calculations because of inadequate staging information (8 from decade 1 [1970-1979], 2 from decade 2 [1980-1989], and 2 from decade 3 [1990-1999]) and/or follow-up in survivors of less than 12 months (4 from decade 2 and 5 from decade 3). The remaining 55 patients form the basis of this study.

The demographics, cancer stage, and method of treatment for all patients were compiled and compared by decade. All radiation treatments were prescribed by and administered in the Department of Radiation Oncology at Oregon Health Sciences University. The main outcome measures were locoregional control of the cancer, crude survival, colostomy-free survival, and morbidity. *Locoregional control* was defined as undetectable tumor in the anorectum, its mesenteric drainage, or inguinal lymph nodes for the duration of surveillance after primary treatment and subsequent salvage treatments. *Major morbidity* was defined as conditions requiring subsequent surgery, National Cancer Institute common toxicity criteria⁹ grades III and IV, and treatment-related death.

Statistical analysis of locoregional control was performed with Fisher exact test. Analysis of crude survival and colostomy-free survival were performed with log-rank test and graphed with Kaplan-Meier product limit curves.

United States and Europe.⁶⁻⁸ While modifications of Ni-gro and coworkers' protocol remain the standard of care today, the addition of mitomycin and the higher doses of radiotherapy do not come without increased morbidity and mortality. This study is intended to determine whether these evolving treatment strategies for anal canal cancer during the past 3 decades have improved crude survival, colostomy-free survival, and local control without increasing morbidity and mortality.

RESULTS

The study population included 55 patients. Ten patients were treated during decade 1, 16 during decade 2,

Table 1. Distribution of Anal Cancer Stage During 3 Decades From 1970 to 1999

Decade	No. of Patients	Cancer Stage, No. (%)				
		I	II	IIIA	IIIB	IV
1970-1979	10	1 (10)	2 (20)	1 (10)	4 (40)	2 (20)
1980-1989	16	2 (13)	9 (56)	2 (13)	2 (13)	1 (6)
1990-1999	29	6 (21)	15 (52)	4 (14)	3 (10)	1 (3)
Overall	55	9 (16)	26 (47)	7 (13)	9 (16)	4 (7)

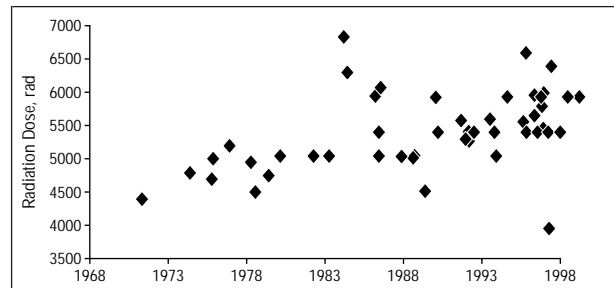


Figure 1. Radiation doses delivered for treatment of anal cancer from 1968 to 1999 (to convert to grays, multiply by 0.01).

and 29 during decade 3. The mean ages (57.3, 58.7, and 57.1 years), sex distribution (40%, 25%, and 38% female), and mean follow-up after treatment (32 [range, 1-120], 51 [range, 0-156], and 43 [range, 6-110] months) were similar across all 3 decades. The distribution of cancer stage is shown in **Table 1**. Three patients were positive for human immunodeficiency virus, and 2 patients were receiving long-term immunosuppression. All 5 of these patients were treated during decade 3.

During the course of the study, 4 different modalities were used as the primary treatment of anal cancer: radiation only, surgery only, sequential therapy (chemotherapy followed by radiation followed by radical surgery), and concurrent chemoradiation. All 4 patients treated by surgery alone underwent abdominoperineal resection. There were no local excisions. The "sequential therapy" protocol consisted of 1 cycle of intra-arterial chemotherapy (doxorubicin hydrochloride or bleomycin sulfate) followed by 4500-6000 rad (45-60 Gy) of external beam radiation, a 6-week treatment break, then reexamination and abdominoperineal resection for persistent disease.

Over time there was a change in the primary treatment modality from sequential therapy to concurrent chemoradiation. Concurrent chemoradiation was administered in a fairly standard fashion. External beam radiation was delivered to the primary tumor site and inguinal areas for 5 to 6 weeks. Fluorouracil was infused during the first and last weeks of radiation, with most patients also receiving mitomycin with the first cycle of fluorouracil. The mean dose of radiation increased from 4790 rad (47.9 Gy) in decade 1, to 5380 rad (53.8 Gy) in decade 2, and 5700 rad (57.0 Gy) in decade 3 (**Figure 1**). **Figure 2** shows the frequency with which each modality was used.

Locoregional control improved during the succeeding decades (50%, 81%, and 93%, respectively; $P=.01$). These improved control rates include successful salvage

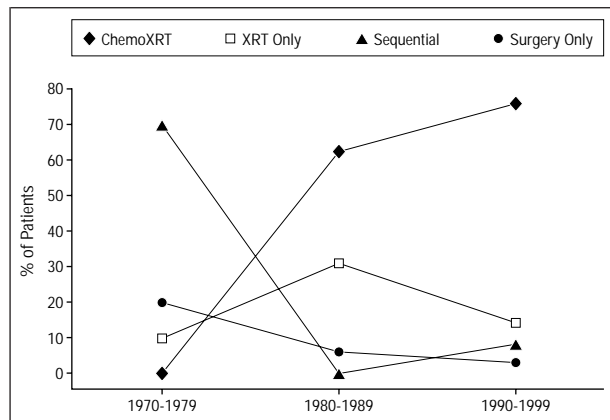


Figure 2. Percentage of patients treated by each primary modality for each decade from 1970 through 1999. ChemoXRT indicates concurrent chemoradiation; XRT only, irradiation only; and sequential, chemotherapy followed by irradiation followed by radical surgery.

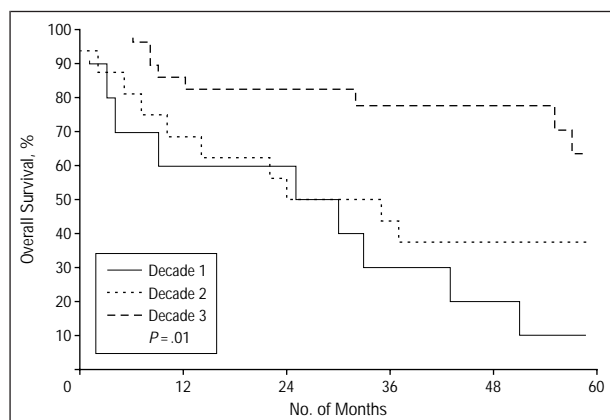


Figure 3. Crude survival after treatment for anal cancer by decade from 1970 through 1999.

therapy in 4 patients (1 sequential chemotherapy and radiation therapy in decade 1, 1 abdominoperineal resection in decade 2, and 2 abdominoperineal resections in decade 3) for locoregional failure. A corresponding improvement was also noted in the 5-year crude survival rate, which increased from 10% during decade 1, to 38% in decade 2, and 64% in decade 3 (**Figure 3**).

Nineteen patients (35%) in this series required a colostomy at some point during their treatment. None was reversed. Eight patients required palliative diverting colostomy for septic complications or incontinence, 4 at time of presentation and 4 during or after primary treatment. The 4 patients who underwent diversion at presentation had perianal sepsis and were discovered to have advanced, perforated anal cancers (1 from decade 2 and 3 from decade 3). In the cases of the other 4 patients, 1 underwent diversion for severe radiation proctitis midway through concurrent chemoradiation (decade 2), 1 underwent diversion for perianal ulcers 4 months after radiation (decade 3), 1 had diversion for incontinence and unresectable tumor 4 months after radiation (decade 1), and 1 had diversion for perianal ulcers and incontinence 3 years after combined chemoradiation (decade 2). From a review of the patients' medical records, it was not possible to determine whether the exact cause of the in-

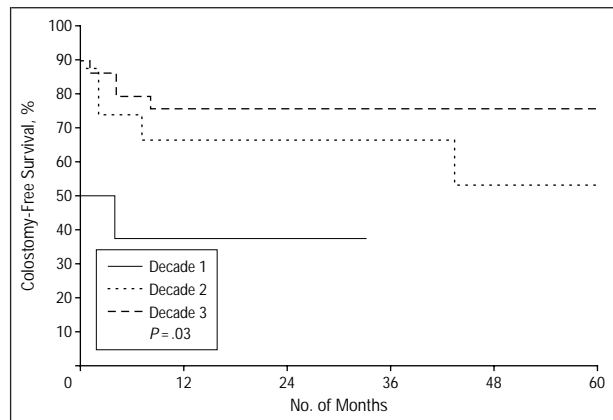


Figure 4. Crude colostomy-free survival after treatment for anal cancer by decade from 1970 through 1999.

Table 2. Complications From Treatment of Anal Cancer From 1970 to 1999

Decade	No. of Patients	No. (%)		
		Minor Complications	Major Complications*	Treatment-Related Deaths
1970-1979	10	4 (40)	4 (40)	1 (10)
1980-1989	16	6 (38)	9 (56)	2 (12)
1990-1999	29	22 (76)	12 (41)	1 (3)

*National Cancer Institute common toxicity criteria grade III or IV,⁹ additional surgery, or treatment-related death.

continence in these patients was loss of rectal compliance, sphincter injury from radiation or direct tumor extension, or change in stool consistency.

Eight patients underwent abdominoperineal resection as part of their primary treatment, 1 of whom had previous palliative colostomy. Five patients underwent abdominoperineal resection for salvage, 1 of whom had previous palliative colostomy. The 2-year crude colostomy-free survival improved over time from 38% in decade 1 to 76% in decade 3 (**Figure 4**).

Complications of therapy were common (**Table 2**). The number of minor complications was higher during the third decade of the study. The most common complications were dermatitis, diarrhea, and stomatitis. The number of major complications (requiring additional surgery, grade III or IV toxicity,⁹ or death) remained constant throughout the study (Table 2). Four patients died of treatment-related complications, 1 in each of the first and third decades and 2 in the second.

COMMENT

The last 30 years of the 20th century saw a major change in the treatment of anal canal carcinoma. These 3 decades represent 3 phases of this development. During decade 1, from 1970 through 1979, most centers were performing radical surgery by abdominoperineal resection as the treatment of choice. At our institutions, surgery was usually preceded by sequential chemotherapy and radiation therapy in an effort to reduce the high local recurrence rate. Midway through this decade, Nigro and colleagues⁴ first re-

ported their success in sterilizing the tumor bed with preoperative concurrent fluorouracil, mitomycin (initially porfiromycin), and low-dose radiation therapy.

Spawned by impressive data from larger case series detailing improved survival, lower local recurrence rates, and the reduction in the number of permanent colostomies, the "Nigro protocol" became the standard of care despite the absence of controlled trials. Decade 2, 1980 through 1989, represents this transitional phase in which concurrent chemoradiation began to replace other forms of therapy for anal canal cancer. Concurrent chemoradiation for curative intent was first used at our institutions in 1982. A modification of the Nigro protocol was used that included a higher dose of radiation therapy (Figure 1).

By decade 3, 1990 through 1999, concurrent chemoradiation had been adopted as the most common treatment modality at our institutions. By this time, large randomized, controlled trials by the United Kingdom Co-ordinating Committee on Cancer Research,⁶ Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group,⁷ and European Organization for Research and Treatment of Cancer⁸ were confirming the importance of the key components of combined treatment. First, the addition of fluorouracil and mitomycin to radiation resulted in reduced local failure and colostomy rates compared with radiation alone.^{6,8} The second question was whether the addition of mitomycin (and its increased toxicity) provided benefit. The Radiation Therapy Oncology Group–Eastern Cooperative Oncology Group, reported by Flam et al,⁷ showed that the addition of mitomycin to fluorouracil and radiation improved the disease-free survival and colostomy-free intervals in patients with anal canal cancer. They also demonstrated that additional chemoradiation can be successful in up to 50% of patients who have a positive biopsy specimen after 4500 to 5040 rad (45.0–50.4 Gy), thereby effectively treating persistent local disease.

Radiation doses for anal cancer at our institution during the past 3 decades have gradually increased. The original Nigro protocol was planned preoperative chemotherapy and 3000 rad (30 Gy) of irradiation. In the early years of using chemotherapy and irradiation (without planned surgery), our institution used doses of 4500 to 5040 rad (45.0–50.4 Gy). As we and others have gained more experience with the chemotherapy and irradiation, we have learned that surgery is not required in most patients who receive 5000 to 5500 rad (50–55 Gy). We now plan to give 5400 rad (54 Gy) to the tumor area for all patients. If there is still palpable residual tumor at that dose, then an additional 540 to 1080 rad (5.4–10.8 Gy) is given to the tumor.

Local persistence or recurrence of any pelvic cancer is a devastating and usually incurable situation. Patients often develop progressive deep pelvic pain as the tumor invades surrounding structures. Direct tumor extension can also lead to infection, obstruction, bleeding, and adjacent organ dysfunction. Our study shows that, by adopting improved treatments, there has been steady improvement in local control of the tumor. Stage alone does not seem to account for this improvement. While one might expect the decreased local control seen in decade 1 because of the higher percentage of advanced-

stage tumors during this period, there continued to be improved local control from decade 2 to decade 3 despite a similar distribution of tumor stages in these 2 periods. Since there was no increase in salvage attempts over the decades, it is unlikely that better follow-up or imaging techniques led to earlier detection or subsequent irradiation of persistent or recurrent disease. With the reduction in the local recurrence rate, it follows that the need for abdominoperineal resection and permanent colostomy has also drastically decreased (Figure 4).

Major treatment complications, including treatment-related deaths, have not increased during the study duration and are similar to those in large trials.⁶ In decade 3, however, we observed a higher rate of minor complications compared with that seen in decades 1 and 2. Most of this added morbidity came in the form of dermatitis. There were only 4 patients with grade 3 or 4 neutropenia (1 of 16 in decade 2 and 3 of 29 in decade 3).

Our study population represents an unselected group of consecutive patients treated for epidermoid carcinoma of the anal canal. Because of the retrospective nature of this study, there was no formalized follow-up schedule for examinations and tests. Only patients who had been followed up by at least a clinical examination for a minimum of 12 months from the completion of their primary treatment were included in the study. This study represents an institutional, longitudinal study over 3 decades; the patients were not treated by one physician or one physician group, but rather by a number of individuals. The timing of follow-up and the decision to perform computed tomography or ultrasound were at the discretion of the treating physician.

This study included veterans, a predominantly male group, and therefore the ratio of men to women was much higher than that seen in other studies. The mean age of our patients remained constant during the study. The number of advanced-stage tumors was higher in decade 1 but similar in decades 2 and 3. Eight of 18 patients with anal cancer in the first decade were excluded because inadequate staging information was available. From the fact that 5 (62%) of these 8 patients died of disease, one can infer that either they presented with advanced stage or did not respond successfully to their treatment. This percentage of treatment failures is similar to that of the 10 patients from decade 1 for whom adequate staging was available (80%).

Our study aimed to examine whether the application of improved treatment techniques over time can improve the quality of life and survival of patients with anal canal cancer. By design, this study did not meet the rigors of a prospective randomized trial. It is not able to analyze whether variables such as better disease awareness and earlier detection, selection bias, or follow-up strategies help to account for the improved outcomes that we have observed. Indeed, these variables are likely to have contributed to the progress. For example, more patients presented in decade 1 with stages III and IV disease than in decades 2 and 3. Nonetheless, this study describes an evolution in treatment during the past 3 decades and documents that patients with anal cancer now have longer crude survivals and fewer colostomies without significant added morbidity.

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Validating statisticians for this study were Motomi Mori, PhD, and Yi-Ching Hsieh, MS.

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DISCUSSION

Richard Billingham, MD, Seattle, Wash: Just to underscore, this is quite an uncommon condition, and if you look at their numbers, they have had 76 patients over 30 years, which comes down only to about 2.5 patients a year. So this is not very common and therefore difficult to study.

They made the appropriate distinction that anal canal cancer is very different from anal margin cancer. Anal margin cancer is that of the perianal skin and is considered and treated more like a skin cancer and is not even tracked by the Cancer Surveillance System. Anal canal cancer has in past years been more common in women. Only 35% of their group were women, but many of these patients came from the VA hospital that has a strongly male predominance.

Twenty-seven percent of their patients were excluded, but being a retrospective study over this period of time, this is certainly expected to have some attrition there. They do report 93% survival in the last decade, but this may represent a very short follow-up in some of the patients done in the last 5 years. In their Figure 3, it suggests that maybe there is only a 62% 5-year survival, but, again, these are crude survivals, not cancer-specific survivals. These cancers tend to occur in elderly patients and there are many intercurrent causes of death, making this further difficult to characterize.

Their concept of a colostomy-free survival is a new one to me. It is very interesting and it hasn't been used to my knowledge by other authors, which makes it difficult to compare this series with a previous series.

In terms of the impact of HIV [human immunodeficiency virus] disease, in 5 patients of their last 29, 3 had HIV disease and 2 were otherwise immunocompromised. Joel Palefsky, from San Francisco, reports a great increase in anal cancer in the gay population with predominantly HIV disease, but this has to my knowledge not been seen outside of San Francisco despite similar rates of HIV disease in other communities. There are many other risk factors for anal canal cancer as well as anal margin cancer, including smoking, anal intercourse, human papillomavirus [HPV] and condylomata, and sexually transmitted diseases.

The goal here in treatment of anal cancer is to avoid colostomy and avoid abdominoperineal resection. In this series, 36% required colostomy, some for symptoms but some of them for primary treatment without the benefit of pretreatment with chemoradiotherapy. It was not entirely clear from the manuscript whether the incidence of the colostomies after chemoradiotherapy has in fact diminished for either symptom. Certainly it has for the primary treatment.

In terms of salvage after chemoradiotherapy, it has been our hope that, if you treat them with chemoradiotherapy, and they don't resolve, an abdominoperineal resection can be done with very good results. Curiously, in past years, less than 30% 5-year survival has been seen in some of these patients who have salvage abdominoperineal resection after chemoradiotherapy.

Complications are still substantial, even in the third decade of the study. Forty-one percent had major toxicity; I am delighted that they have broken out major toxicity from minor toxicity here. Many studies report their complications and the people who are more honest simply report more complications, and we don't have a good way to stratify major vs minor, and I am glad that they were able to do this. Interestingly, only 1 of the 29 in this last decade had a treatment-related death, so while they did have major toxicities, they were able to salvage all but 1 of the 29.

My questions for the authors include: how do the groups do when they are analyzed by the treatment rather than by the decade? The decade approach is very interesting, but I hope in the final manuscript they will also have a look at this by treatment type. Is there any benefit to be gained by a different chemotherapeutic regimen? When Nigro proposed this, he was using fluorouracil and mitomycin, which had been used for adenocarcinoma. Cisplatin has enjoyed some currency and success in squamous carcinomas of the head and neck, and several institutions are now using this without good data for the chemotherapy for anal cancer, and for colostomy-free survival, are we really doing better now and avoiding colostomies after chemotherapy and radiation therapy, or does this have simply to do with the shorter follow-up interval?

Theodore X. O'Connell, MD, Los Angeles, Calif: I have several questions regarding the radiation dose. Certainly the original protocol by Nigro uses 3000 rads, which was quite successful. It seems in this study that they started with a higher dose and then have escalated this over time. The question is, why did they do this? Were they having bad results with the 3000 rads? Certainly the combination of 3000 with the mitomycin and the fluorouracil is synergistic.

One of the reasons to use the 3000 is that, as you escalate the dose, you have more complications, and I notice that they had a 40% major toxicity. I was wondering if this is related to the higher-dose radiation. Also, they have a relatively high incidence of palliative colostomy. Is this due to radiation complications because of the higher dose due to fistulizations, ulcers, etc?

Certainly when we do use a higher dose, it's because of T3 or T4 lesions, which again may have higher complications in their own right. This is done with interstitial radiation. Is this why they have the higher dose and is part of their radiation therapy dose interstitial besides external beam?

William P. Schecter, MD, San Francisco, Calif: I have 3 questions. One relates to the epidemiology and the 35% inci-

dence of anal cancer in women. In San Francisco we have greater than a 2:1 ratio of male to female, similar to Oregon. My question is, how many of these patients had evidence of HPV disease? How many of them had a history of anoreceptive intercourse? I noticed that only 5 were HIV positive. Were all of the patients in the last 15 years tested for HIV disease?

I also have a question about the radiation therapy. Our radiation therapists at UCSF don't follow the Nigro protocol either and routinely give up to 6000 rads. I have seen an occasional patient who has been incapacitated by radiation proctitis. Do we really need to give these very high doses of radiation therapy?

Finally, I am going to ask a question challenging conventional wisdom. Although there is a difference between the transitional epithelium in the anal canal and the squamous epithelium at the anal verge cancer, is there really a difference between anal canal squamous cancer and anal verge cancer, or is it that we are just diagnosing the cancers at the anal verge earlier and able to give them more effective treatment?

Sherry M. Wren, MD, Stanford, Calif: Did you find that any of the pathologic subtypes, such as cloacogenic or basaloïd, were better or worse prognostic indicators in this disease? Secondly, what are you advocating for routine follow-up? Did you perform routine blind biopsies?

Theodore R. Schrock, MD, San Francisco: How do you determine persistence after completion of therapy? Do you biopsy routinely? If you detect persistence, how do you treat it? Are you pushing the dose of radiation up, and, if so, how far? Or are you automatically going to abdominoperineal for salvage? Lastly, were the groins included in your initial radiation fields? And how do you treat groin metastases if they appear?

Chris De Virgilio, MD, Torrance, Calif: One, conventional wisdom states that we want to avoid colostomy at all costs, but a recent study from the *Annals of Surgery* suggests that patients with a colostomy had improved quality of life compared to patients with a very low anterior resection. So my question to you first is, did you look at quality of life in these patients and compare the quality of life in patients who may have avoided colostomy at all costs but perhaps had other local complications as a result of this high-dose radiation?

Second, did you analyze the patients from each decade stage by stage to see if you really did make a difference in your intervention?

Thomas R. Russell, MD, Chicago, Ill: It's a nice historical review of the treatment. Bear in mind that, even before 1970, abdominoperineal resections were being done as well as bilateral groin dissections. I would like to point out that, in my experience in San Francisco, the demographics of this disease really have changed dramatically from primarily women to mostly men, from older patients to younger patients, and of course the whole HIV immunosuppressive era, and association with the papillomavirus. This was another example where we can consider lifestyles of patients after treatment, since few patients want colostomies. Granted, in the last 2 decades the tumors were diagnosed in earlier stages, but it appears this is another example of the decreasing need for the use of colostomy yet maintaining results.

Since this is a junctional tumor, was there any adenocarcinoma mixture with the epidermoid type of pathology?

Dr Deveney: I have been assigned a big challenge. I have been writing down notes feverishly, so I hope I can answer all of these very fine questions that have been asked of us. I want to congratulate my junior partner, Dr Whiteford, on his fine presentation of this unusual type of cancer. Of course, with the small numbers that will accrue in any institution, even over a 30-year period, it is somewhat difficult to analyze by treatment rather than by decade. In order to be meaningful, one must really break it down by stage, and when we break down by stage we see the usual expected improved survival by stage, but in trying to compare one decade to another, when you break it

out by stage, you really have too few patients in any group to really see a statistical improvement.

Was there any improvement in the colostomy-free numbers? Yes, indeed, there was over the 3 decades, and it does reflect, as Dr Russell commented, a change not just in our treatment but also in adhering to patient wishes in many cases. We were successful in progressively decreasing the number of colostomies that were required by decade, and the main reason for doing a colostomy in the earlier decades was the use of abdominoperineal resection as the primary treatment modality after chemo and radiotherapy, and in the later years it was for patients who presented with advanced tumors and had either septic complications of their tumor itself prior to treatment or incontinence because of the advanced nature of the tumor, or obstruction. In no case was a colostomy needed because of the toxicities of the radiation treatment itself.

Dr Billingham asked whether our results were any better with chemo and radiotherapy in the latter decade or was it only because of shorter follow-up. As we pointed out in the presentation, the length of mean follow-up in all 3 decades was essentially identical at 36 months.

Dr O'Connell asked why the radiation dose has increased from that proposed by Nigro, and this really is an evolution in all of the centers where randomized trials were done, both in the United States and in Europe. The doses were more commensurate with the doses that have been used by our radiation oncologists, and they are in that 4500 to 5500 range rather than in the 3000 initially reported by Nigro. As I mentioned, there were no colostomies due to radiation complications. We did not use interstitial radiation therapy in any of the patients.

Dr Schechter commented on the difference, which we also noticed, having lived in San Francisco earlier, that a higher incidence of patients with epidermoid cancer of the anal canal were men and had HIV, and he asked whether all of the patients in the latter decades had been tested. Since this was a retrospective study, that information was not always available, and they were not routinely tested. Also, there were a few HPV-associated squamous cancers in our group, but it was a very small number.

He also asked a very good question about whether there is a difference between anal canal and anal margin cancers or is it really only a matter of earlier detection of the tumors. It may in part be true that patients present earlier with anal margin tumors, but stage for stage there does appear to be a much worse outcome with anal canal cancers than anal margin cancers.

Dr Wren asked whether there was any difference in survival in the subtypes, and we did not see any difference among those with squamous, pure squamous, basaloïd, or cloacogenic, which actually represented a very small number in our otherwise already small series.

Dr Wren and Dr Schrock asked about how we monitor the patients in follow-up for persistent or recurrent disease. We do not routinely do blind biopsies at the conclusion or at 4 to 6 weeks after the conclusion of the radiation therapy. We do biopsies based on any suspicion whatsoever of persistent disease. We ourselves follow the patients very closely every 3 to 6 months for any evidence of recurrence of disease, at which time they are biopsied. If a patient has persistent disease or local recurrence, the dose of radiation is pushed up as high as 7000 or an abdominoperineal resection is done, depending on the consent and discussion with the patient regarding that. The groins are included in the radiation fields routinely. Because this was a retrospective study, to answer Dr De Virgilio's question, we were not able to look at the quality-of-life issues, and also stage by stage, as I mentioned before, our numbers are really too small to do a subset analysis. In answer to Dr Russell's other question, we had no adenocarcinomas or mixed adenosquamous carcinomas in our group.