INTERVIEW

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Tracks 1-11

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Track 3	Evolving radiation therapy techniques in H&N cancer
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Track 2

DR LOVE: Can you discuss the findings from RTOG-0129, comparing conventional versus accelerated radiation therapy and concurrent cisplatin for patients with Stage III or IV squamous cell carcinoma of the head and neck?

DR ROSENTHAL: In this trial, all the patients received cisplatin, and they were randomly assigned to receive either standard fractionation — five fractions a week for seven weeks for a total dose of 70 Gray — or concomitant boost treatment, which delivers approximately the same total dose, 72 Gray, in six weeks (Ang 2007). The question is whether, in the setting of concurrent chemotherapy, it is advantageous to accelerate the radiation therapy.

The study closed three years ago, and the data are now maturing. We hope to have efficacy data in time for ASCO 2009. The preliminary safety data suggested that while some increase in mucositis and earlier acute toxicities occurred, the risk of some of the more worrisome consequential toxicities, such as dysphagia and longer-term feeding-tube dependency, is not increased (Ang 2007).

A study from Germany several years ago asked a similar question, but in that study all of the patients received accelerated fractionated radiation therapy and were randomly assigned to receive chemotherapy or not (Staar 2001). No improvement in survival outcomes occurred for the group that received both therapies, and almost half of the two-year survivors on that arm were feeding-tube dependent.

Therefore, I believe we need to be careful in using these aggressive chemoradiation therapy regimens until we have a clear signal of safety and efficacy. In my practice, I prefer to use concurrent chemotherapy with once daily radiation therapy until we see an advantage in accelerating radiation therapy.

Track 8

DR LOVE: What's your take on the role of cetuximab in the treatment of head and neck cancer?

DR ROSENTHAL: The improvement in locoregional control and survival with cetuximab when combined with radiation therapy (Bonner 2006; [3.1]) is similar to the data seen when combining cytotoxic chemotherapy and radiation therapy. Remarkably, the data for cetuximab in combination with radiation therapy showed no increase in mucositis, feeding-tube requirements or Grade III dysphagia (Bonner 2006; [3.2]).

The main scenario where I consider this agent off study now is for patients who are ineligible for cisplatin as a radiation sensitizer. Another involves the patient with a more borderline tumor, in which the physician may feel uncomfortable using radiation therapy alone but is hesitant to add the toxicities of concurrent chemotherapy.

Much debate has taken place regarding how we might use cetuximab instead of chemotherapy. We don't have data directly comparing cetuximab to cisplatin as a radiation sensitizer. The results of the study comparing cetuximab with radiation therapy to radiation therapy alone (Bonner 2006; [3.1]) seem to be as good as the data from the trials in which chemotherapy was used.

DR LOVE: Is there any situation in which you would use the combination of cetuximab, chemotherapy and radiation therapy in clinical practice?

DR ROSENTHAL: I don't recommend it, and labeling specifically recommends that it not be used. We typically don't do it, even in our academic setting, where sometimes we use more aggressive therapies.

One published study combined accelerated radiation therapy, chemotherapy and cetuximab, and it closed early due to untoward toxicities. However, positive outcomes were observed with the combination, and some of the toxicities probably could have been prevented had we known about some of the electrolyte-wasting properties, such as hypomagnesemia (Pfister 2006). Ultimately we might use this strategy, but I believe we need to wait for trials to validate its safety and efficacy.

3.1

Phase III Randomized Trial of High-Dose Radiation Therapy with or without Cetuximab for Patients with Locoregionally Advanced Squamous Cell Head and Neck Cancer: Efficacy Data

Protocol IDs: UAB-9901, NCT00004227
Accrual: 424 (Closed)

Eligibility
- Stage III or IV squamous cell carcinoma of the oropharynx, hypopharynx or larynx
- No distant metastases
- No prior therapy

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- High-dose radiation therapy x 7 to 8 weeks
- High-dose radiation therapy x 7 to 8 weeks + cetuximab weekly during radiation therapy

	Radiation therapy and cetuximab (n = 211)	Radiation therapy alone (n = 213)	Hazard ratio (95% CI)	*p*-value*
Median duration of locoregional control	24.4 months	14.9 months	0.68 (0.52-0.89)	0.005
Median progression-free survival	17.1 months	12.4 months	0.70 (0.54-0.90)	0.006
Median overall survival	49.0 months	29.3 months	0.74 (0.57-0.97)	0.03

* Log-rank test; CI = confidence interval

SOURCE: Bonner JA et al. *N Engl J Med* 2006;354(6):567-78. **Abstract**

Track 10

DR LOVE: What about the role of induction chemotherapy?

DR ROSENTHAL: Induction chemotherapy took hold after data from The Department of Veterans Affairs Laryngeal Cancer Study Group suggested it had a clear role in organ preservation (The Department of Veterans Affairs Laryngeal Cancer Study Group 1991). Subsequent trials then showed that despite an improvement in response, even complete response, it did not ultimately affect locoregional control or survival.

Recently we have seen trials evaluating more active drugs and combinations in the induction setting. Two Phase III trials — TAX-323 and TAX-324 — evaluated cisplatin/5-FU with or without docetaxel in patients who were to receive radiation therapy. Both trials reported improved survival with the addition of docetaxel (Vermorken 2007; Posner 2007; [2.2, page 10]). ■

3.2

Radiation Therapy with Cetuximab for Squamous Cell Head and Neck Cancer

"An exceptional feature of this randomized, phase 3 trial, which was carried out among patients with head and neck cancer who were treated with curative intent, was the finding of a survival advantage associated with the use of a molecular targeting agent, cetuximab, delivered in conjunction with radiation.

We found that the addition of cetuximab to high-dose radiotherapy significantly increased both the duration of control of locoregional disease and survival among patients with locoregionally advanced head and neck cancer.

With the exception of acneiform rash and infusion-related events, the incidence rates of severe (grades 3, 4, and 5) reactions were similar in the two treatment groups. Notably, cetuximab did not exacerbate the common toxic effects associated with radiotherapy of the head and neck, including mucositis, xerostomia, dysphagia, pain, weight loss, and performance-status deterioration."

SOURCE: Bonner JA et al. *N Engl J Med* 2006;354(6):567-78. **Abstract**

SELECT PUBLICATIONS

Ang K et al. **A Phase III trial to compare standard versus accelerated fractionation in combination with concurrent cisplatin for head and neck carcinomas (RTOG 0129): Report of compliance and toxicity.** *Proc ASTRO* 2007;**Abstract 21**.

Bonner JA et al. **Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck.** *N Engl J Med* 2006;354(6):567-78. **Abstract**

Curran D et al. **Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab.** *J Clin Oncol* 2007;25(16):2191-7. **Abstract**

The Department of Veterans Affairs Laryngeal Cancer Study Group. **Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer.** *N Engl J Med* 1991;324(24):1685-90. **Abstract**

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Pfister DG et al. **Concurrent cetuximab, cisplatin, and concomitant boost radiotherapy for locoregionally advanced, squamous cell head and neck cancer: A pilot phase II study of a new combined-modality paradigm.** *J Clin Oncol* 2006;24(7):1072-8. **Abstract**

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Staar S et al. **Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy — Results of a multicentric randomized German trial in advanced head-and-neck cancer.** *Int J Radiat Oncol Biol Phys* 2001;50(5):1161-71. **Abstract**

Vermorken JB et al. **Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer.** *N Engl J Med* 2007;357(17):1695-704. **Abstract**