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Approach to & Management of Recurrent Head & Neck Cancer

BY KEVIN WOOD, MD, & EVERETT VOKES, MD

Recurrent head and neck cancer is a major cause of morbidity and mortality. For patients who present with locoregional recurrence, salvage surgery, or re-irradiation represent possible curative approaches and can be considered on a case-by-case basis. For more extensive or metastatic disease, options are limited to palliative systemic therapy or supportive care. In this latter setting, first-line systemic therapy leads to median overall survival of around 10 months, with patients with p16 expression or positive HPV status having improved outcomes with a trend toward statistical significance. Patients who have had recurrent disease diagnosed within 6 months of platinum-based chemotherapy have a significantly shorter median overall survival of 6 months or less.

CME Article

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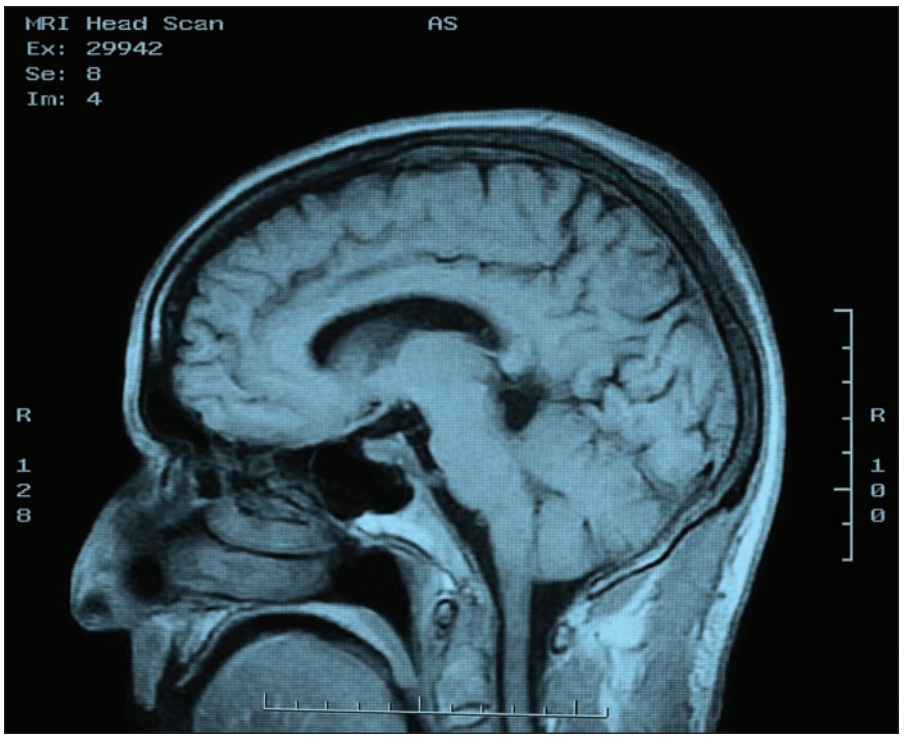

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Prospective Case Review in Radiation Oncology Prior to Treatment Delivery

BY AMISHI BAJAJ, BA, ABHISHEK A. SOLANKI, MD, MS, & WILLIAM SMALL, JR., MD, FACR, FACRO, FASTRO

Quality and safety are key tenets in radiation oncology. Part of a robust quality management program within a radiation oncology department is peer review of patients undergoing radiation treatment.

Peer review, defined as "the process whereby providers evaluate the quality of their colleagues' work to ensure that prevailing care standards are met," (*J Oncol Pract* 2016;12(3),196-198) is a critical aspect of quality assurance in the practice of radiation oncology and allows for consistent, standardized, and guideline-concordant care to be delivered to patients. Prior studies investigating the impact of peer review have found that radiation therapy plans that deviate from standard protocols have been found to be associated with inferior outcomes relating to cancer control and survival.

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Uncovering a New Subtype of Acute Lymphoblastic Leukemia

An international research team led by St. Jude Children's Research Hospital investigators has uncovered details of a new, high-risk subtype of acute lymphoblastic leukemia (ALL), as well as a possible targeted therapy. The findings appear in *Nature Communications* (2016;7:13331 DOI: 10.1038/ncomms13331).

The subtype is characterized by chromosomal rearrangements that involve the MEF2D gene and one of six partner genes, most often the gene BCL9. It is called MEF2D-rearranged ALL.

"MEF2D is a transcription factor that switches on expression of other genes during normal development," said corresponding author Charles Mullighan, MD, MBBS, a member of the St. Jude Department of Pathology. "We found that MEF2D chromosomal rearrangements disrupt expression of those genes and create a vulnerability to at least one targeted therapy, the drug panobinostat."

Genomic analysis of more than 1,700 children, adolescents, and adults with ALL identified 42 with MEF2D rearrangements. Researchers calculated that MEF2D-rearranged ALL accounts for 5.3 percent of the almost 30 percent of ALL cases whose genetic basis was unknown. The MEF2D-rearranged subtype occurred most frequently in adolescents and was associated with reduced survival compared to some other ALL subtypes.

Treatment Stops Leukemic Cells

Panobinostat inhibits the activity of a family of proteins including HDAC9. Researchers showed that MEF2D-rearranged leukemic cells produced

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PERIODICALS

Approach to & Management of Recurrent Head & Neck Cancer

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Management of Locoregional Recurrence

Options for patients with locoregional recurrence include surgical resection if a small, isolated mass is staged. The extent of recurrent disease is significant in dictating likelihood of cure and length of overall survival after surgical resection. In a large meta-analysis, median survival was in excess of 24.3 months for limited, isolated disease but decreased to 9.3 months for more extensive disease (P = 0.0006). Reported 5-year overall survival rates after salvage surgery range from 11 to 39 percent.

There is minimal data regarding indications for adjuvant re-irradiation combined with chemotherapy after salvage surgery. A phase III trial demonstrated an improvement in disease free survival, but not overall survival, with adjuvant therapy in unspecified patients after salvage surgery. This study had strict inclusion criteria and the majority of patients did not have nodal disease. A small French study demonstrated 4-year survival rates of 43 percent (95% CI 25-62) after adjuvant re-irradiation combined with chemotherapy in patients with positive surgical margins and/or extracapsular extension. Finally, a phase II study suggested the strategy of using induction chemotherapy prior to salvage surgery as a strategy to determine which patients would be appropriate for further aggressive adjuvant therapy, but larger studies need to be carried out.

The indication for prophylactic neck dissection after salvage surgery remains unclear. A retrospective analysis of 68 recurrent laryngeal patients demonstrated 28.3 percent of patients had pathologic nodal disease. Higher rates were seen in supraglottic and transglottic sites (60% and 30%, respectively). Higher incidences and benefit from neck dissection also have been noted in patients with neck metastasis at initial diagnosis, patients with larger recurrent tumors (T3/4), and in recurrences detected occurs within 1 year of therapy. Prophylactic neck dissection is generally recommended in the setting of these higher risk patients.

For those with more extensive recurrent disease who are deemed unresectable, either chemoradiation or palliative systemic therapy are possible options. The location of the primary, extent of disease, prior therapies, and performance status must be taken into account when making these decisions. The challenges of treating recurrent disease are significantly increased in patients whom have a recurrence or second primary in a previously irradiated field. For these patients, a complex task for the treating multidisciplinary team is deciding if an aggressive, but possibly curative, approach is possible using chemoradiation. In a large retrospective study of re-irradiated patients, a performance status of 0-1 was a significant prognostic factor PFS and OS, and a trend toward significance with both OS and locoregional control was noted with two or fewer recurrences.

Management of Metastatic Recurrence

Possible options in the metastatic setting include cytotoxic chemotherapy, checkpoint inhibitor immunotherapy, and molecularly targeted compounds. Patient-specific factors, including performance status and prior therapy, must be taken into account when deciding on an appropriate therapeutic regimen. Independent unfavorable prognostic factors affecting overall survival include weight loss of >5%, ECOG performance score of 1 (versus 0), well/moderate tumor cell differentiation, a primary tumor in the oral cavity or hypopharynx, and prior radiation therapy.

Cytotoxic Chemotherapy

Currently, standard of care for patients with good performance status includes platinum-based doublet chemotherapy, plus cetuximab. Common cytotoxic regimens include:

- platinum agent (cisplatin or carboplatin) + fluorouracil
- platinum agent + paclitaxel
- platinum agent + docetaxel

Phase III studies demonstrate similar response rates of around 30 percent with the above regimens. While treatment with two cytotoxic drugs have been shown to increase response rate as compared to single-agent therapy, no improvement in overall survival has been noted. There is no evidence that three or four drug cytotoxic chemotherapy regimens improve overall survival.

The addition of cetuximab is based on the phase III EXTREME trial demonstrating a prolongation in overall survival with chemotherapy plus cetuximab significantly compared with chemotherapy alone (median 10.1 versus 7.4 months, HR for death 0.80, 95% CI 0.64-0.99). Significant improvements were also seen in the progression-free survival and objective response rates (median 5.6 versus 3.3 months and 36 versus 20%, respectively).

High-powered studies comparing the efficacy of cisplatin versus carboplatin are lacking. Indirect evidence from the EXTREME study showed no apparent difference in results between patients treated with the two platinum regimens. However, a Southwest Oncology Group trial demonstrated a non-statistically significant improvement in response rate (32% versus 21%) and overall survival (7 versus 5 months) for the cisplatin-containing regimen.

For patients with poor performance status, cetuximab plus doublet chemotherapy is generally contraindicated and single-agent therapy versus palliative care can be considered. Immunotherapy may increasingly be considered as a reasonable option in this specific population, though evidence is currently lacking.

Immunotherapy

Genes involved with inflammation are frequently found to be mutated in patients with HNSCC (*Clin Cancer Res* 2015;21:632-641) and the presence of tumor-infiltrating lymphocytes has been noted in 40 percent of tumors (*Clin Cancer Res* 2015:21:870-881). In the relapsed setting, recurrence and metastases of head and neck cancer has been demonstrated to be promoted by immune evasion (*J Clin Oncol* 2015;33:3293-3304). This pre-clinical data suggested that immunomodulatory drugs may have efficacy for this disease, which has now been confirmed with both pembrolizumab and nivolumab in the platinum-refractory setting.

Pembrolizumab, 200mg every 3 weeks, was approved by the FDA in August 2016 for patients with recurrent or metastatic head and neck squamous cell carcinoma who have had progression on or after platinum-based chemotherapy. This is a conditional approval based on KEYNOTE-012, a phase 1b study demonstrating objective response rates in 18 percent of patients (8 of 45; 95% CI 8 – 32) (*Lancet Oncology* 2016;17(7):956-65). Responses were independent of HPV status. Seventy-eight percent of the tumors were PD-L1-positive. Phase III studies (NCT02252042 and NCT02358031) are ongoing.

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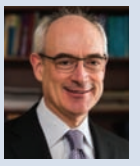

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Learning Objective for This Month's CME Activity: After participating in this CME activity, readers should be better able to identify treatment options for recurrent and metastatic head and neck cancer.

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Nivolumab demonstrated an improvement in overall survival compared to standard, single-agent therapy in the CHECKMATE-141 study (*N Engl J Med* 2016;375:1856-1867). The study demonstrated in a significant improvement in overall survival (7.5 months versus 5.1 months, HR for death, 0.70; 97.73% CI, 0.51 to 0.96; p = 0.01). The rate of progression-free survival at 6 months was 19.7 percent versus 9.9 percent. Nivolumab thus represents the first agent to improve overall survival in the platinum refractory setting.

Targeted Agents

Targeted therapy options include the anti-EGFR monoclonal antibody, cetuximab, and a number of small molecule tyrosine kinase inhibitors (TKIs). The two most extensively studied TKIs in head and neck cancer are afatinib and gefitinib.

Phase III trials of cetuximab have demonstrated a response rate of approximately 10 percent in the platinum refractory setting. In one study of 103 patients, the median survival with cetuximab after progression on platinum-based therapy was 7.5 months, with 13 percent of patients having an objective response (*Clin Cancer Res* 2015:21:870-881). The standard dose for cetuximab is 250 mg/m2 weekly, with further dose escalations not showing clinical benefit.

> Outcomes remain poor in the recurrent or metastatic setting, though new data from clinical trials evaluating immunotherapy are demonstrating improvements on prior standards of care.

The clinical role of tyrosine kinase inhibitors is less clear. In a phase III trial comparing gefitinib to weekly IV methotrexate, overall survival rates were similar regardless of therapy (6 months). In a phase III trial comparing gefitinib plus docetaxel versus placebo plus docetaxel, no difference in overall survival was seen. Afatinib did demonstrate an improvement in progression-free survival (median 2.6 months versus 1.7 months, hazard ratio [HR} 0.80, 95% CI 0.65-0.98), although not in overall survival when compared to methotrexate (*Lancet Oncol* 2015;16(5):583).

Management of Oligometastatic Disease

Patients presenting with recurrent disease with a limited metastatic burden (generally three sites or less) can be considered for aggressive local therapy for all sites of disease. Studies have demonstrated 5-year overall survival rates of 32-34 percent for patients treated with surgical metastasectomy. Stereotactic radiation therapy is a reasonable alternative to surgical metastasectomy. Site of primary disease appears to influence outcomes, with patients with a primary tumor from the oral cavity having significantly worse prognosis. For instance, in a series of 23 patients with oral tongue SCC, 96 percent relapsed with a median time to death of 10 months.

Future Directions

Outcomes remain poor in the recurrent or metastatic setting, though new data from clinical trials evaluating immunotherapy are demonstrating improvements on prior standards of care. Many immunotherapy and targeted therapeutic options are currently under investigation in the recurrent or metastatic setting, with a selection of notable trials summarized in the **Table**. Future clinical trials will focus on whether first-line immunotherapy in the metastatic setting may improve outcomes compared to cytotoxic chemotherapy, and whether combining multiple immunotherapy agents may improve response rates and durations.

Our 2016 Approach

At the University of Chicago Medical Center, our multidisciplinary team approaches locoregional recurrences aggressively with a curative intent in the appropriate patient. Whenever possible, these patients are treated on a clinical trial, such as our current trial evaluating nab-paclitaxel-based re-induction chemotherapy followed by response-stratified chemoradiotherapy (NCT01847326). Outside of a clinical trial, we often employ the THFX regimen (paclitaxel, hydroxyurea, 5-flourouracil plus twice daily radiation), though another option would be twice-daily radiation plus cisplatin and paclitaxel based off RTOG 9911 data.

For metastatic disease, a similar approach of placing all appropriate candidates on an available clinical trial, often involving an immunotherapy single-agent or combination regimen, whenever possible is used. If a trial is not available and performance status remains appropriate, our metastatic patients with excellent performance status are treated first-line with doublet chemotherapy with the EXTREME regimen (platinum-agent + cetuximab + either 5-FU or Paclitaxel), followed by an immunotherapy agent at time of progression. OT

TABLE: Enrolling Immunotherapy Clinical Trials

Currently enrolling phase II and III clinical trials specifically for head and neck cancer patients involving immunotherapy agents. Different drugs are indicated by shading. (*Lancet Oncology* 2016;17(7):956-65)

Identifier	Drug	Phase	Setting
NCT02358031	Pembrolizumab versus SOC	III	First-line for Recurrent or Metastatic
NCT02538510	Pembrolizumab + Vorinostat	II	Inoperable recurrent or metastatic
NCT02289209	Pembrolizumab + Reirradiation	II	Inoperable locoregional
NTC02369874	MEDI 4736 +/- Tremelimumab versus SOC	III	Recurrent or Metastatic
NCT02551159	KESTREL trial: MEDI 4736 +/- Tremelimumab versus SOC	III	Recurrent or Metastatic
NCT02499328	MEDI 4736 + either AZD9150 (STAT3 inhibitor) or AZD5069 (CXCR2)	II	Metastatic
NCT02741570	Nivolumab + Ipilimumab versus SOC	II	First-line for Recurrent or Metastatic
NCT02684253	Nivolumab + SBRT versus Nivolumab alone	II	Metastatic
NCT02823574	Nivolumab + Ipilimumab versus Nivolumab + placebo	II	Recurrent or Metastatic
NCT02543645	Atezolizumab + Varlilumab (anti-CD27 antibody)	I/II	Metastatic
NTC02655822	CPI-444 (adenosine-A2A receptor target) +/- atezolizumab	I	Metastatic
NCT02274155	MEDI6469 (OX40 antibody)	I	Metastatic
NCT02643550	IPH2201 (Monalizumab) + cetuximab	II	Recurrent or Metastatic