

LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA (SCCA) OF CHEEK

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CASE PRESENTATION

This is the case of a 45 year old female with no previous comorbidities, who initially presented with right cheek swelling. Biopsy of the lesion showed infiltrating, well-differentiated squamous cell carcinoma.

CT Scan of her neck was done (Fig. 1a, b): which showed large heterogeneously enhancing highly vascular mass measuring 6.3 x 5.6 x 7.6 cm showing vascularity and

areas of necrosis was seen on right side of the cheek. It was extending into the right maxillary sinus, nasal cavity, nasopharynx and tonsillar pillar. It was abutting the tongue with loss of fat planes. There was erosion of walls of right maxillary sinus, hemimandible, maxilla and pterygoid plates. Superiorly, it was involving pterygoid muscles and infratemporal fossa and inferiorly it was extending into the floor of mouth, overlying skin, right temporomandibular joint and parapharyngeal space. Parotid gland was

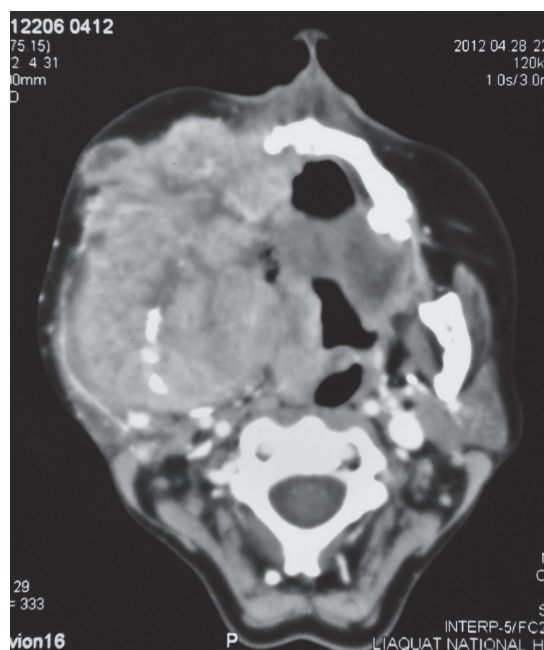
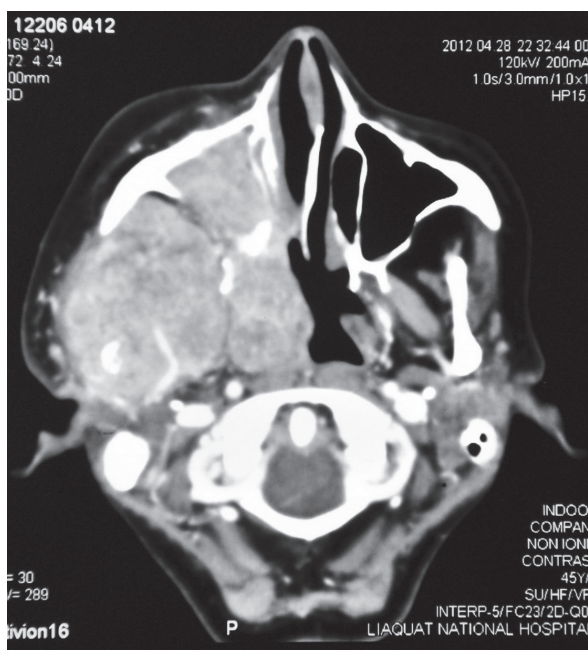


Fig. 1 (a,b) CT Scan neck with IV contrast, axial image showing heterogeneously enhancing mass involving Rt bucal mucosa extending into Rt maxillary sinus, nasal cavity, nasopharynx and Rt tonsillar pillar.

stretched by the mass and was inseparable from it. Multiple enlarged necrotic lymph nodes were seen on right side at level II and one of them measured 2.6 x 1.7 cm.

Since it was unresectable (T4b Stage IV), medical oncologist recommended concurrent chemoradiation. Radiation oncologist deferred at this stage because of extensive field of radiation therapy and it was decided to give induction chemotherapy.

Because of her poor performance status, she was given a weekly dose of carboplatin and paclitaxel. She received chemotherapy for six weeks and then CT scan was repeated (Fig. 2 a,b).

Marked regression of disease was seen. Mass showed reduction in size and measured 3.4 x 3.2 x 4.6 cm. Necrotic lymph nodes now measured 1.9 x 0.9 cm. The patient was then put on concurrent chemoradiation with cisplatin and received 40 fractions of radiation over 6 weeks.

CT scan performed 6 weeks post radiation showed (Fig. 3 a,b) further reduction in the size of the mass which measured 2.6 x 2.2 x 2.5 cm. The necrotic lymph now measured 1.0 x 0.7 cm. There was again the involvement of right pterygoid muscle, parapharyngeal soft tissue, erosion of right hemimandible and maxilla as previously seen. The

other areas previously involved appeared clear. There was a dramatic response after the chemotherapy but the question was if the mass was a residual tumour or scar tissue.

TUMOUR BOARD DISCUSSION

Participants included an ENT surgeon, two medical oncologists, a radiation oncologist, a pathologist and a radiologist.

How should this patient be managed further?

- Surgery
- Additional chemotherapy
- Additional radiotherapy
- Observation with imaging

In spite of a remarkable tumour response to chemoradiation, the possibility of residual disease remained. PET CT could identify active residual disease and additional chemotherapy may delay relapse of the disease. However, PET CT would not be able to detect microscopic disease and further chemotherapy may not improve survival. Surgical resection was not possible due to the location of the residual tissue. Further radiation therapy was also not an option because the patient had already received the maximum dose (8000 cGy).

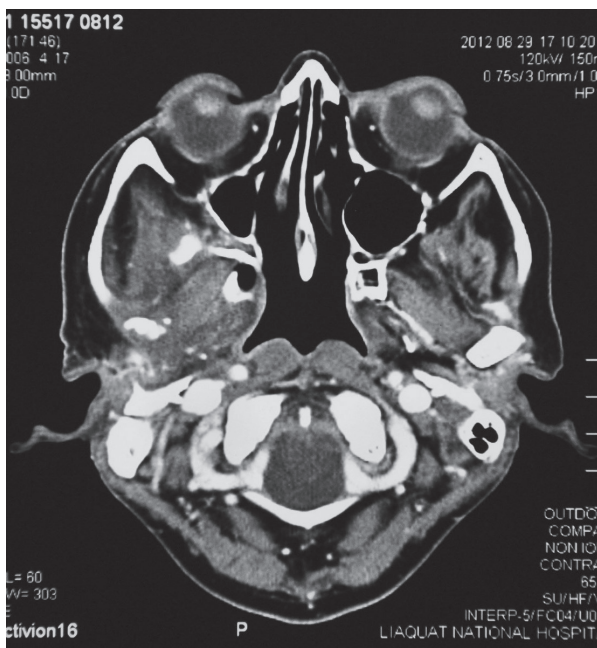


Fig. 2 a,b. CT Scan neck with IV C contrast axial images showing marked regression of disease. Residual disease is now only seen in Rt buccal mucosa.

It was concluded that the goal would be to reduce the morbidity from the malignancy. PET CT may be used to detect any active residual disease which, if present, would warrant further chemotherapy. Thereafter, the disease should be observed for recurrence with serial CT imaging at 6-8 weeks intervals with clinical follow ups.

OVERVIEW

ENT SURGEON'S PERSPECTIVE

The American Joint Commission on Cancer (AJCC), according to its revised classification of 2002, separated the most advanced T stage of various sites of head and neck into T4a and T4b. Their purpose for such a subdivision of T4 tumours into two subgroups was, to emphasize the poor prognosis and high rate of unresectability of T4b tumours. Most tumours with T4b classification would be generally categorized as unresectable. They should, therefore, not be offered radical surgical treatment but should be offered medical treatment with palliative intent, be it with chemotherapy, radiation or a combination. On the other hand, T4a tumours were also advanced disease that would require extensive surgery but were classified as resectable tumours.

T4a versus T4b classification for oral cavity tumours

T4a: Tumour invades adjacent structures, bone, muscle of tongue, Maxillary sinus, facial skin

T4b: Tumour invades masticator space, pterygoid plates or skull base and/or encases internal carotid artery

This patient's case comes under the category of very advanced head and neck cancer. CT scan reveals extension into masticator space (MS) as well as involvement of pterygoid plates (PP). Both these anatomic sites are deeply situated and a surgical approach is often difficult to pursue. It will not be possible to achieve an oncologically adequate surgical margin. Prognosis in such cases is quite dismal and would not justify a surgical approach.

MEDICAL ONCOLOGIST'S PERSPECTIVE

The rationale for chemoradiation and chemotherapy is to increase local control by overcoming radioresistance and to eradicate systemic micrometastasis. The clinical CR rate obtained with concurrent cisplatin and radiation therapy (single daily fraction) in patients with locally advanced head and neck cancers is in the range of 65% to 70%.

Despite the initial response and high local control rates with radiation therapy, more than 80% of these patients

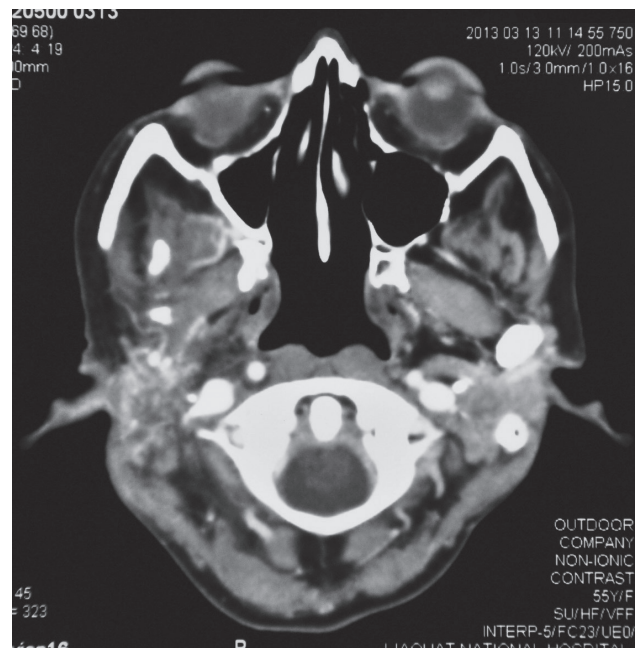
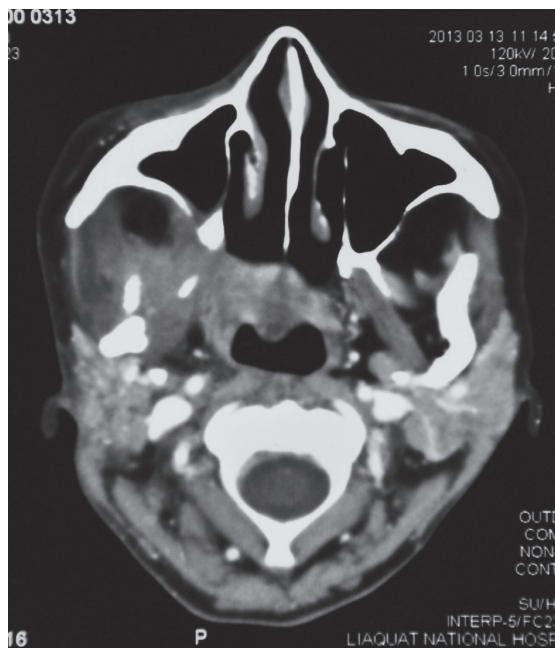


Fig. 3 a,b. CT scan Neck with IV contrast axial images showing further resolution of disease. No mass is seen in nasopharynx, Rt maxilla or nasal cavity.

recur within 2 years, and the 5-year survival is poor. In an attempt to improve outcomes for radiation therapy, altered-fractionation schemes have been investigated. [1-6] Among the altered-fractionation schema investigated were hyperfractionation regimens and accelerated regimens. The Budach and Bourhis meta-analyses have demonstrated local and regional control using altered fractionated radiation equivalent to that seen with concurrent chemoradiotherapy. In addition, the Budach meta-analysis reported that concurrent chemoradiotherapy with any radiation fractionation schedules resulted in a statistically significant survival benefit of 12 months and an absolute survival gain of 13% to 15% at 2 years. [7]

At least seven prospective phase III trials comparing concurrent chemotherapy-radiation therapy vs radiation therapy have been reported [8-14]. All were positive in favor of the combined-therapy arm. In the Intergroup study (SWOG and ECOG) for locally advanced and unresectable head and neck cancers, patients were randomized into three arms: (1) single-agent cisplatin every 3 weeks during radiation therapy, (2) cisplatin 5FU with radiation therapy, or (3) radiation therapy alone. Standard daily fraction radiation therapy was given to all patient groups. The 3-year survival rates were 37%, 29%, and 20%, respectively. The difference was only statistically significant ($P=.016$) between cisplatin plus radiation therapy and radiation therapy alone.

In order to improve the results further, the question of induction chemotherapy came.

Induction chemotherapy is the chemotherapy given before definitive local treatment, i.e. concurrent chemoradiation. Induction chemotherapy may improve local control, while also reducing the rate of distant metastases that may not be adequately treated by local therapy or by lower-dose chemotherapy as part of chemoradiotherapy. However, the efficacy of induction chemotherapy in prolonging survival remains to be conclusively proven. A long-term study of 237 patients with nonmetastatic stage III or stage IV SCCHN who received four cycles of induction chemotherapy with cisplatin and 5-fluorouracil (5-FU) (PF) followed by locoregional treatment (surgery and/or radiotherapy) or locoregional treatment alone. Survival rates at 5 and 10 years were 21% (95% confidence interval [CI], 12.3%–30.1%) and 16% (95% CI, 7.7%–23.9%), respectively, for the induction chemotherapy plus locoregional treatment group and

8% (95% CI, 1.5%–12.3%) and 6% (95% CI, 0.1%–9.1%), respectively, for the locoregional treatment alone group (log rank $p=.04$). EORTC 24971/TAX 323 phase III trial compared TPF with PF as induction chemotherapy before radiotherapy in 358 patients with locoregionally advanced, unresectable stage III or stage IV SCCHN [14]. For the primary endpoint, progression-free survival, the median times were 11.0 months in the TPF group and 8.2 months in the PF group, at a median follow-up of 32.5 months. Treatment with TPF resulted in 27% lower risk for death (p value 0.02), with a median survival time of 18.8 months, compared with 14.5 months in the PF group. Grade 3 or 4 neutropenia and leukopenia were more common in the TPF group, and severe thrombocytopenia and anemia were more common in the PF group.

Whereas TAX 324, which was a randomized, open label Phase III trial comparing 3 cycles of TPF to 3 cycles of PF followed by 7 weeks of chemoradiotherapy, showed a better 5 year overall survival of 52% with TPF compared to 42% in those receiving PF. Median survival was also better with TPF (70.6 months) versus PF (34.8 months) [15]

2 Phase III randomized clinical trials PARADIGM and DECIDE failed to show any benefit in overall survival with induction chemotherapy prior to chemoradiation. [16, 17]

Interestingly in both the studies the 3 year overall was much higher than expected for all treatment arms. This improved overall survival could have masked any benefit from induction chemotherapy. The authors thought that this could be secondary to increased incidence of HPV related oropharyngeal cancer which has a better prognosis and patients in this trial were not stratified according to Human Papilloma Virus (HPV).

Therefore based on the PARADIGM and DECIDE trial it won't be justified to say that induction chemotherapy does not benefit patients with head and neck cancers. Infact further studies with stratification according to HPV status are needed.

EXPERT'S COMMENTS

It is certainly an interesting case and a huge tumour. In spite of its size, I assume no systemic metastasis at presentation. The treatment plan and sequence are my choice of care. But the best Induction Chemotherapy is the triple agents and the most used is the TPF. My

strong recommendation is the modified TPF, Taxotere 75 mg/m² IV day one, Carboplatin AUC 5.0 IV day one, 5FU 2,600 mg/m² 24 hour infusion days 1, 8, and 15. To repeat all the three agents every three weeks for three courses. This will produce the best response possible, and more important, the least toxicities of N&V, renal, peripheral neuropathy, hearing, mucositis, and water and electrolytes.

The best concurrent CT+RT is weekly Carboplatin AUC 2.0 with no Induction Chemotherapy, or 1.5 after Induction Chemotherapy to be given on the first day of RT and then weekly to two-three weeks after RT. Again, this will produce the least toxicities and the best response possible.

My recommendation for this patient is additional three courses with the modified TPF and then close follow up and more prayers.

She may need to be seen and evaluated every three months for two years, or as clinically indicated, then every six months for three years or as clinically indicated, and then yearly or as clinically indicated.

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