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Protection of Oral Mucosa in Patients With Oral Tongue Squamous Cell Carcinoma Treated Postoperatively With Intensity Modulated Radiotherapy

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Purpose: To present initial results of protection of oral mucosa aiming to reduce the severity of acute oral mucositis in postoperative intensity modulated radiotherapy (IMRT) patients with oral tongue squamous cell carcinoma compared to IMRT without oral mucosa sparing.
Methods and Materials: A total of 48 patients with oral tongue squamous cell carcinoma who received postoperative IMRT in our institution were randomized to two groups: the oral sparing group and oral unsparing group. For the oral sparing group (24 patients), the patients had distinctive sparing of the oral mucosa outside the planning target volume (PTV). The main spared site that with a dose of <32 Gy as far as possible was the portion of the mucosa including bilateral cheeks, upper lip and lower lip mucosa that was defined as the united site. For the oral unsparing group (24 patients), the protection of the oral mucosa was not intended. The severity of clinical acute mucositis of each patient in the united site and the 3 other oral sites (contralateral oral tongue, hard palate and soft palate) was assessed weekly during IMRT until complete healing. Oral mucositis grading was performed based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE). Dosimetry in each oral site and some therapeutic measures related to acute mucositis between the two groups were compared.
Results: During IMRT, there no grade 4 and more acute mucositis in all oral sites in this study. As compared with oral unsparing group, the incidences of grade 3 and 2 mucositis in the united site were significantly lower in the oral sparing group (0% and 25%, respectively, vs. 45.8% and 54.2%, respectively, $p = 0.000$). Dosimetric analysis revealed that the mean dose to the united site was significant reduce with oral sparing than without oral sparing (41.8±7.4 Gy vs. 58.8±2.2 Gy, $p = 0.000$). The oral sparing IMRT was associated with significant reduce in using of analgesics ($p = 0.043$) and intravenous antibiotics ($p = 0.039$), those related to severity of acute mucositis, including mouth pain and infections.
Conclusions: Use of oral sparing IMRT for postoperative patients with oral tongue carcinoma resulted in significant decrease in severity of acute mucositis in the oral sparing site and leaded to less symptoms and benefits in terms of quality of life preservation.

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Radiotherapy After Hyperbaric Oxygen Concurrent With Superselective Intra-arterial Carboplatin Chemotherapy Enhances Survival of Patients With Oral Cancer

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Background: A hypoxic cell fraction within a tumour tissue decreases the effect of radiotherapy and chemotherapy and gives a poor prognosis. Because the oxygen tension of tumour tissues remains higher than that of normal tissue after hyperbaric oxygen (HBO) exposure, recent study suggests that irradiation within 15 min after HBO exposure enhances the antitumour effect of radiotherapy in malignant tumours. We retrospectively evaluated the effect of HBO given concurrently withintra-arterial carboplatin chemoradiotherapy in patients with oral cancer.
Patients and Methods: At our institution, 125 patients with oral cancer, including those with recurrent lesions or cervical lymph node metastasis, were treated with superselective intra-arterial carboplatin infusion, external beam radiotherapy, UFT (tegafur–uracil) and/or surgery between April 1995 and January 2011. Treatment was combined with HBO for 62 patients and 63 were treated without HBO exposure. HBO was administered in a multiplace hyperbaric chamber according to the following schedule: 13 min of compression with air, 60 min of oxygen inhalation using an oxygen mask with a reservoir at 2.5 atmospheres absolute, and 10 min of decompression with oxygen inhalation. Radiotherapy was performed five times weekly immediately after HBO exposure.
Results: Details of patient characteristics and treatment outcomes are summarized in Table 1. Of the 56 patients whose tumours were treated with chemoradiotherapy without surgery, 32 also received HBO (CR-wHBO group) and 24 were treated without HBO (CR-woHBO group). Of the 63 patients whose tumours were resected after preoperative chemoradiotherapy, 29 received HBO (S-wHBO group) and 34 were treated without HBO (S-woHBO group). The disease-specific survival rate of patients treated with HBO (66%) was significantly higher than that of patients treated without HBO (42%) ($p = 0.009$). In addition, the five-year disease-specific survival rates were: S-wHBO group, 80%; S-woHBO group, 65%; CR-wHBO group, 57%; and CR-woHBO group, 27%. A log-rank test showed that the differences between the survival rate of each group were significant ($p = 0.007$).
Conclusion: These results suggest that radiotherapy after hyperbaric oxygen concurrent with intra-arterial carboplatin chemotherapy enhances the survival of patients with oral cancer, and that HBO is a useful adjunct to chemoradiotherapy for squamous cell cancer of the oral cavity.

Table 1. Characteristics of the 125 patients and treatment result

	without HBO (63 tumours)	with HBO (62 tumours)	p value
Gender			0.707
male	40	42	
female	23	20	
Age	66.7±10.1	67.6±9.8	0.611
T classification			0.022
T0	0	5	
T1	1	2	
T2	16	26	
T3	6	3	
T4	32	24	
rT2	1	1	
rT3	60	1	
rT4	5	0	
Tx	2	0	
N classification			0.258
N0	30	35	
N1	12	9	
N2	19	18	
N3	1	0	
rN1	1	0	
Carboplatin dosage (mg)	476±120	455±109	0.338
Pretreatment hemoglobin level (g/dl)	12.90±1.97	13.04±1.76	0.886
Irradiated dose (Gy)	43.8±18	48.7±18.6	0.145
Surgery of primary tumour			0.284
Yes	34	29	
No	26	33	
Prognosis			0.001
No evidence of disease	23	41	
Alive with disease	0	1	
Died of their disease	34	15	
Died of another disease	6	5	

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Phase II Study of Cetuximab With Concomitant-boost Radiotherapy (RT) in Japanese Patients With Locally Advanced Squamous Cell Carcinoma of the Head and Neck (LA-SCCHN)

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Background: The multinational randomized phase III study demonstrated the significantly improvement of OS, response rate in cetuximab + RT group compared to RT alone for LA-SCCHN (Bonner et al. 2006). We conducted a phase II, open-labeled, multicenter study in Japanese patients with locally advanced SCCHN in order to assess feasibility, safety and efficacy of cetuximab treatment in combination with concomitant-boost RT regimen.
Material and Methods: Patients with stage III or IV SCCHN arising in the oropharynx, hypopharynx, or larynx, which is expressing EGFR, were enrolled. The treatment period was 7 weeks (Week 1 to 7). Cetuximab was initiated with 400 mg/m^2 from Week 1, followed by weekly infusions of 250 mg/m^2 from Week 2 to 7. RT was initiated from Week 2 to 7 (i.e.

72.0 Gy in 42 fractions/6 weeks). The primary endpoint was the treatment completion rate of patients who completed ⩾ 70% of the cetuximab planned dose administration (in terms of the relative dose intensity of cetuximab) and the full dose of radiotherapy ⩽ 2 weeks over the planned schedule (in terms of radiotherapy duration ⩽8 weeks).
Results: From Mar 2009 until Jan 2010, 27 pts were screened. Of them, 22 pts were enrolled and treated (ITT population). Patients characteristics of ITT population: median age (years), 67.0 (range, 53 to 81); male/female, 21/1 pts; oropharynx/hypopharynx/larynx, 6/8/8 pts; stage III/IV, 12/10 pts. The median duration of cetuximab treatment was 7.9 weeks (range, 7 to 9), and that of RT was 44.0 days (range, 40 to 52). All 22 pts completed the treatment, and the completion rate was 100% (95% CI: 84.6%, 100.0%). The response rate (CR+PR) post RT was 81.8% (assessed by the independent committee). All pts experienced AEs. Most common AEs with grade 3/4 were mucosal inflammation (16pts, 72.7%), dermatitis (6pts, 27.3%), infection, radiation skin injury and stomatitis (each in 5 pts, 22.7%).
Conclusions: The completion rate (100%) and the response rate (81.8%) are comparable to those of the cetuximab + RT group in the multinational randomized phase III study (Bonner et al. 2006). AEs were consistent with the underlying disease, administration of RT or cetuximab. The study results demonstrate that cetuximab + RT is well-tolerated, a feasible and efficacious treatment in Japanese pts.

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Helical Tomotherapy in the Treatment of Locally Advanced Squamous Cell Oral Carcinoma

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Background: The aim of this study is the evaluation of toxicity and response to the treatment of patients affected with locally advanced carcinoma of the oral cavity, irradiated by Helical Tomotherapy.
Materials and Methods: From February 2008 to January 2011, 87 patients with head-neck cancer were treated by Helical Tomotherapy. Among them, 20 presented locally advanced squamous cell carcinoma of the oral cavity and were treated with radical intent: 12 underwent concomitant radiochemotherapy with weekly administration of Carboplatin and 8 exclusive radiotherapy for comorbidities.
Median age was 67 years (39−87) and male/female ratio 3:1. Regarding anatomic subsyte, oral tongue, floor of the mouth, gingiva, retromolar trigone primary tumours, were 8, 6, 1, 5, respectively. Stage of disease at diagnosis was III in 2, IVA in 16 and IVB in 2 cases.
Simultaneous Integrated Boost (SIB) technique in 30 fractions was used, delivering 66 Gy (RT-CT)/67.5 Gy (RT) to PTV1 (PET positive oral region), 60−63 Gy to PTV2 (oral cavity and PET positive nodes), 54 Gy to PTV3 (negative cervical nodes). Contouring was performed on the basis of a CT/PET/MR image fusion. Planned Adaptive module was used in consideration of anatomical changes occurred during the therapy.
Results: All patients completed radiotherapy, without any interruption due to the treatment. Concerning acute toxicity, G2 dermatitis, dysphagia and mucositis were registered in 25%, 40% and 55% of cases, respectively.
Median follow up was 16 months (range 3−29). Response on primary tumour and positive nodes was achieved in all patients, in terms of clinical and nuclear/radiological findings: complete in 16 (80%) and partial in 4 (20%). One year after the end of the treatment, no significant difference between RT-CT and RT was noted.
Conclusion: Helical Tomotherapy allows to obtain favourable local control and low acute toxicity in locally advanced squamous cell carcinoma of the oral cavity.

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Results of Postoperative Radiotherapy in Patients With Salivary Duct Carcinoma of the Major Salivary Glands

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Background and Purpose: Salivary duct carcinoma (SDC) is a rare malignancy of high grade pathologic type. Currently, there are no confirmed prognostic variables in the management of SDC. We evaluated clinical outcomes and prognostic factors in 35 patients with SDC treated with postoperative adjuvant radiation, and investigated postoperative adjuvant RT role.
Materials and Methods: We retrospectively assessed overall survival (OS), locoregional control (LRC), and disease-free survival (DFS) in 35 patients with SDC of the major salivary glands who underwent surgery. Neck dissection was performed in 31 patients (88.6%). All patients received postoperative adjuvant RT to tumour bed and ipsilateral neck node. Prescribed median dose was 59.4 Gy (range, 50.4–71.4 Gy). Factors evaluated for prognosis included gender, age, symptom duration, tumour site, tumour size, TNM classification, and pathologic features; perineural invasion (PNI), lymphovascular invasion (LVI), extra-parenchymal invasion, and resection margin status. The median follow-up period was 43 months (range, 7–155 months).
Results: Of the 35 patients, 30 (85.7%) were male: median age at initial diagnosis was 62 years (range, 38−75 years). The parotid gland was mainly affected in 22 patients (62.9%). Eighteen patients (51.5%) had pathologic T3/T4 tumours, and 26 patients (74.3%) showed pathologic nodal involvement. The actuarial 3-year locoregional control, disease-free survival, overall survival rates were 75.8%, 55.7%, and 79.5%, respectively. Cause specific death rate was 31.4% (n = 11). Pathologic nodal involvement was correlated with distant metastasis ($p = 0.011$). Lymphoovascular invasion was significant prognostic factor of distant metastasis-free survival ($p = 0.049$), locoregional control ($p = 0.012$), and overall survival ($p = 0.003$) in the Cox proportional hazard model, whereas perineural invasion was significant prognostic factor only of overall survival ($p = 0.005$).
Conclusions: Despite high nodal involvement rate, loco-regional control was successful. Surgery and postoperative radiotherapy were effective for locoregional control. Lymphovascular invasion and perineural invasion were significant prognostic factors for patients with SDC.

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Treatment Outcomes of Radiotherapy for Tonsillar Carcinoma in the Era of Intensity-modulated Radiotherapy

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Background: We performed this study to analyze treatment outcomes and to evaluate prognostic factors in patients with tonsillar carcinoma who were treated with radiotherapy (RT).
Materials and Methods: We retrospectively reviewed 164 patients with tonsillar carcinoma treated with RT between January 1979 and September 2009. Of the 164 patients, 91 were treated with 2-dimensional RT (2D-RT), 46 were treated with 3-dimensional conformal RT (3D-CRT), and 27 were treated with intensity-modulated RT (IMRT). When patients were treated with IMRT, simultaneous integrated boost was used. Thirty patients were treated with RT alone, 40 patients were treated with chemotherapy and RT (CRT), 66 patients were treated with surgery and RT and/or chemotherapy (SRT), and 28 patients were treated with concurrent chemoradiotherapy (CCRT). Bilateral neck irradiation was delivered to 141 patients, and ipsilateral neck irradiation to 23 patients. In definitive RT, median dose was 70 Gy (range, 51−71), 70 Gy (54−74), and 67.5 Gy for 2D-RT, 3D-CRT, and IMRT, respectively. In postoperative RT, median dose was 64.8 Gy (range, 54–70.2), 66 Gy (54−70), and 63 Gy (60–67.5) for 2D-RT, 3D-CRT, and IMRT, respectively. Acute and late toxicity were graded according to the Radiation Therapy Oncology Group radiation morbidity scoring criteria.
Results: The median follow-up time was 42 months (range, 2–288). The 5-year locoregional progression-free survival (LRPFS), distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival (OS) rates were 86%, 94%, 82%, and 80%, respectively. In the univariate analysis, 5-year DFS rate was associated with the RT technique (2D-RT, 77%; 3D-CRT, 82%; IMRT, 100%, $p = 0.035$), T stage (T1−2, 87%; T3−4, 74%, $p = 0.036$), and treatment modality (RT alone, 55%; CRT, 78%; SRT, 92%; CCRT, 92%, $p < 0.0001$). In the multivariate analysis, advanced T stage and treatment modality were statistically significant prognostic factors in DFS rate. None of the patients who were treated with ipsilateral neck irradiation experienced relapse in contralateral neck nodes. After the completion of RT, patients who were treated with 2D-RT, 3D-CRT, IMRT, ipsilateral neck irradiation, and bilateral neck irradiation experienced grade ⩾2 xerostomia 91%, 58%, 59%, 35%, and 78%, respectively. At least 6 months of follow-up, patients who were treated with 2D-RT, 3D-CRT, IMRT, ipsilateral neck irradiation, and bilateral neck irradiation experienced grade ⩽1 xerostomia 52%, 76%, 78%, 98%, and 63%, respectively.
Conclusions: In selected patients with well lateralized tonsillar carcinoma, ipsilateral neck irradiation can be an alternative to bilateral neck irradiation, regarding DFS rate and complications. There was no failure when patients were treated with IMRT, but long-term follow-up is needed to evaluate the