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Phase II trial of gemcitabine and paclitaxel (GEMTAX) combination in recurrent or advanced squamous cell carcinoma of the head and neck

O. Kucuk[1], J. Fontana[2], J. Ensley[3]. [1]*Wayne State University, Karmanos Cancer Institute, Detroit, USA;* [2]*Wayne State University, Karmanos Cancer Institute, Detroit, USA;* [3]*Wayne State University, Karmanos Cancer Institute, Detroit, USA*

In preclinical and clinical studies, gemcitabine and paclitaxel have shown activity against squamous cell carcinoma of the head and neck (SCCHN). We have initiated a phase II study in patients with recurrent and/or advanced SCCHN to investigate the efficacy and toxicity of gemcitabine 3000 mg/m2 iv in 30 min and paclitaxel 150 mg/m2 iv in 180 min (GEMTAX) administered biweekly (on days 1 and 15 of each 28-day cycle) as described by Rothenberg et al. (Ann Oncol 9:733-738, 1998). 27 patients on the study had received 1-2 previous chemotherapy regimens, 34 patients had previous radiation therapy and 31 had previous surgery. Ten patients had received previous cisplatin and 5-fluorouracil and 17 had concurrent radiation and cisplatin chemotherapy given as postoperative adjuvant therapy. 218 cycles of chemotherapy was administered to 41 patients. Patients received 0-20 cycles (median 5) of the study treatment. Survival ranged from 1 to 28+ months (median 15). Twelve patients had grade 3 toxicities (9 anemia, 2 neutropenia and 7 infection). There was no grade 4-5 toxicity. Among the 31 response-evaluable patients, 3 had complete response (10%), 15 had partial response (48%), with an overall objective response rate of 58%. Eight patients had stable disease (26%) and 5 had progressive disease (16%) after 4 cycles of treatment. Ten patients were unevaluable for response because they received less than 4 cycles of therapy (required for response evaluability) or were lost to follow-up or had no repeat CT scan to evaluate response. The biweekly administration of gemcitabine and paclitaxel at the prescribed doses was extremely well tolerated with little or no toxicity even though relatively large doses of the two drugs were administered. This regimen appears to have remarkable activity in advanced and/or recurrent SCCHN. Current studies are investigating the pharmacokinetics, pharmacodynamics and possible bone marrow protection when the drugs are administered on days 1 and 15, instead of days 1 and 8, which is customary for most regimens employing gemcitabine.

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Long term results of radiotherapy for T1 glottic carcinoma

G. Dickie, J. Askew, J. Keller, L. Tripcony. *Royal Brisbane Hospital, Oncology, Brisbane, Australia*

A review was undertaken of all, 726 patients with stage T1 glottic squamous cell carcinoma treated between 1961 to 1996. The 5 year results are:

Overall survival (death any cause)	77%
Overall survival (cause specific)	92%
Relapse free survival	87%
Local control (freedom from local relapse)	89%

The 10 year local control results were similar.

The main factor affecting outcome was year of presentation with patients in the latest decade having a significantly better outcome than in the earlier period. Other factors examined included substage, age, sex, histological grade, radiation dose and field size.

Of those who relapsed locally, salvage was successful in 69%.

Severe complications occurred in five cases, 4 necrosis and one carotid stenosis.

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Merkel's cell carcinoma: our experience

L. Ciuffreda[1], V. Caliendo[2], N. Birocco[1], V. Dongiovanni[1], A.M. Ronco[2], L. Fanchini[1], G. Macripò[2], O. Bertetto[1]. [1]*H.S.Giovanni Battista-Molinette, Medical Oncology, Turin, Italy;* [2]*H. S. Giovanni Battista - Molinette, Dermatologic Surgery, Turin, Italy*

Merkel's cell carcinoma is a very uncommon cancer, located in the basal layer of the epidermis and in the hair follicules, occurring mostly in white, elderly people. It usually grows rapidly and is able to give distant metastases and regional lymph node involvement, and often local recurrences occur. Because of these charachteristics the prognosis is often poor even when a medical treatment is feasible according to the age and the conditions of the patient. We are able to give data about twelve patients, followed by the Divisions of Medical Oncology (since 1998) and Dermatology (since 1991) of Molinette Hospital. Seven of them are women, five are men, according to the literature that describes the same incidence between men and women; the age at the diagnosis was comprised between 63 and 94. In six of them the primary lesion was on the thight, in three on the cheek; in the other three the site was respectively shoulder, neck, sculp. After the excision of the primary lesion, six of them had to undergo the dissection of the regional lymph node because of secondary localizations. The two who underwent a profilactic dissection of them, followed by radiotherapy, have never had recurrence, and are nowadays with no evidence of disease at 3 and 7 years from the diagnosis. Five of them were also submitted to chemotherapy with Platinum compounds, Etoposide and Doxorubicin, two women with adjuvant intent, and three men in order to control a rapidly progressing illness; all of the men have died but for two of them it is difficult to give conclusions about the causes of death, because they also had a NHL; we don't know if the concomitance in two patients of a NHL is of any relevance; surely these tumor cells often present different histological patterns, one of which is "lymphoma-like diffuse type of growth". Seven patients are alive, disease free, after a follow up ranging from 9 years to 1; five of them underwent regional lymph node dissection. This seems to confirm that surgical approach must be extended to the lymph-glands, and that radiotherapy must follow surgery. Chemotherapy can slow the evolution of a recurrent disease, but, because of the small number of patients, we are not able to say if it can modify disease free survival and overall survival.

Endocrine tumours

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Prospective randomized multicenter trial on adjuvant percutaneous radiotherapy in locally advanced differentiated thyroid cell carcinoma

A. Schuck[1], M. Biermann[2], C. Poremba[3], W. Boecker[3], A. Heinecke[4], W. Koepcke[4], N. Senninger[5], H. Dralle[5], N. Willich[1], O. Schober[2]. [1]*Radiotherapy, Univ. of Muenster, Muenster, Germany;* [2]*Nuclear Medicine, Univ. of Muenster, Muenster, Germany;* [3]*Pathology, Univ. of Muenster, Muenster, Germany;* [4]*Medical Informatics, Univ. of Muenster, Muenster, Germany;* [5]*Surgery, Univ. of Muenster and Halle/Wittenberg, Muenster and Halle/Wittenberg, Germany*

Purpose: In locally advanced differentiated thyroid cancer (DTC), the role of adjuvant radiotherapy in addition to best standard care (surgery, ablative I-131 therapy, and TSH suppressive therapy) has not yet been sufficiently defined. Some retrospective analyses demonstrated improved local control while others documented similarly good treatment results without adjuvant percutaneous irradiation. We have initiated the first prospective randomized trial addressing this question.

Methods: Patients with differentiated papillary or follicular thyroid cancer in stages pT4 pN0/1/x M0 R0/1 between 18 and 70 yrs. are included in the study. All patients undergo thyroidectomy, central cervical lymph node dissection, and ablative radioiodine therapy. Patients are randomized to receive adjuvant percutaneous irradiation or not. Radiotherapy doses are chosen depending on stage and resection status with an application of 50,4 - 54 Gy to the lymph node areas of the neck and the upper anterior mediastinum and 59,4 - 66,6 Gy to the thyoid bed. Toxicity is evaluated with the RTOG/EORTC score. Quality of life is evaluated with QLQ C-30 of the EORTC. A central review of pathology slides, surgical reports, and radiotherapy plans is performed.

Results: The trial was started in October 2000. So far 49 centers in Germany and Austria are participating, and 63 patients have been included until April 2001. No unexpected toxicity or adverse events have occurred so far.

Discussion: A prospective randomized trial has been initiated to define the role of adjuvant percutaneous irradiation in locally advanced DTC. Assuming continued good recruitment, the study will for the first time allow a definite answer on the clinical utility of this treatment modality.

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Pediatric thyroid cancer

G.L. Lukács[1], F. Győry[1], F. Juhász[1], Sz. Szakáll[2]. [1]*First Department of Surgery;* [2]*Institute of Pathology, University of Debrecen, Debrecen, Hungary*

Purpose: The biological behaviour – and so the extent of surgery – of childhood and adult thyroid carcinomas is controversial. The authors give

account of their epidemiological, clinical and pathological findings and surgical results obtained in 35 years.

Methods: In the years 1965–2000 forty-two children under 18 were operated on. Mean age: 14.8 years, two children were under 10. The rate of incidence is 5.1% of that for all thyroid carcinoma operations of the total age group (n = 818). The most frequent case was papillary carcinoma (32), there were 7 follicular and 3 medullary carcinomas. Cervical lymph node metastases occurred in 19 (45%). Characteristic histological changes were revealed in a comparative study for the pre- and post-Chernobyl periods. Cytofluorimetry was used to determine the DNA-content of tumorous cell nuclei for each type.

Results: 30 patients underwent total or near-total thyroidectomy. Surgical management of lymphatic metastases varied from regional node excision to radical neck dissection. Long-term mortality rate: 2.4% (n = 1), 25 years after surgery. Recurrence: local 3, lymph node 10, liver 1. There was significant increase in childhood and juvenile carcinomas after Chernobyl ($p < 0.05$). The moderate aneuploidy in tumor cell DNA-distribution differs from that of adults.

Conclusions: 1. Predominant in the childhood are papillary carcinomas and this structure is getting more frequent after Chernobyl. 2. Regional lymph-node metastases are common, but despite their DNA-aneuploidy do not influence prognosis. 3. Distant metastases are rare, with hardly any metastasis in bone. 4. The benign course of disease necessitates longer than 20 years follow-up.

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Thyroid cancer in children exposed to Ionizing radiation in Belarus as a result of the Chernobyl accident

L. Harabets[1], V. Drozd[1], Y. Demidcik[2], V. Minenko[3]. [1] *Research and Clinical Institute of Radiation Medicine and Endicrinology, Thyroidology, Minsk, Belarus;* [2] *Minsk State Medical Institute, Oncology, Minsk, Belarus;* [3] *Research and Clinical Institute of Radiation Medicine and Endocrinology, Dosimetry and Radiation Situation, Minsk, Belarus*

Non-effective and delayed iodine prophylaxes made possible the accumulation of radioactive iodine in the thyroid gland in population suffered from the Chernobyl accident. The purpose of the study was to analyze an association between thyroid cancer spread (operation data) and estimated dose on the child thyroid in different regions of Belarus.

Subjects and Methods: 265 verified cases of childhood thyroid cancer were analyzed. Female -male ratio was 1,4: 1. Thyroid dose was estimated by using the empirical model. Average age of children at the accident was 3,0 ±0,1 years old, at the moment of diagnosis - 11,0 ±0,2. Latent period was 8,0 ± 0,4 years.

Results: Out of 265 cases 51,7% children operated on for thyroid carcinoma lived in the Gomel oblast the moment of accident, 28,7%- in Brest oblast, 11,7% - Minsk oblast and 7,9% - in the rest three oblasts. According to estimations average thyroid dose was 0,89 ± 0,06 Gy. Children from Gomel oblast received the highest thyroid dose that was 1,38 ± 0,10 Gy ($p<0,001$) compared with those who were from Brest oblast - 0,48 ±0,03 Gy and form Minsk oblast - 0,08 ± 0,01 Gy ($p<0,01$). Distributions of pT categories among children living in different regions of Belarus at the accident showed that the frequency of pT4 was approximately similar in Gomel, Minsk and Brest oblasts - 42,4%, 50% and 48,4%, respectively. There was a tendency of the increase in the pT2 frequency from Gomel oblast (22,7%), Brest oblast (23,7%) to Minsk oblast (35,5%) although it was not significant. The occurrence of pT1 was significantly higher among children from Gomel oblast (34,5%) compared with those from Minsk oblast (16,1%) while the latent periods in children with different pT categories did not differ (7,7-8,4 years).

Conclusion: Received data suggest that there might be an association between doses received to the thyroid and tumor sizes in children operated on for thyroid cancer but further study needs to be done.

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Papillary thyroid carcinoma - importance of elective lymph node dissection in staging and therapy

R. Dzodic, I. Markovic, M. Inic, M. Kocic, M. Juskic, M. Vlajic. *Institute of Oncology and Radiology of Serbia, Surgery, Belgrade, Serbia, YU*

Introduction: The numerous literature data have shown that lymph node metastases in papillary thyroid carcinoma (PTC) strongly impact the occurrence of relapse.

Aim: Aim of this study was to evaluate the impact of elective lymph node dissection in precise staging and therapy of disease.

Patients and Methods: From 1981. to 2000. we have operated 236 patients with PTC. Age: 44.6±14.3 years at diagnosis (Median 44; Rang 7-80). Sex ratio: F/M-3.7/1, a)Total thyroidectomy (TT) with efective dissection of central and lower jugular lymph nodes of the neck for frozen-section histology was performed in 181 (76.7%) pts. b) TT without lymph node dissection was done in 46 pts; c) palliative surgery for locally advanced cancer in 9 pts.

Results: At the time of diagnosis 41% of patients had enlarged lymph nodes in the neck, either palpable or visible on ultrsound. In the group of 181 patients where elective lymph node dissections were peformed lymph node metastases were found in 130 (71.8%) patients. Out of these 116 pts, were presented with metastases in lower jugular nodes, on forzen-section, so modified radical neck dissection (MRND) was performed in the same act. In the group of patients without elective lymph node dissection (46), relapse occurred significantly erlier in 19 years follow-up (p=0.016).

Disscusion: The impact of lymph node metastases on survival rate in PTC is still controversial. Otherwise, lymph node metastases strongly influenced the earlier occurrence of relapse. Approximately 33% to 45% of patients with papillary thyroid cancer has cervical lymph nodes involved at the time of diagnosis. In studies were more extensive surgery with elective lymph node dissections were performed, the incidence of micrometastases in lymph nodes increases up to 80%. In our series the incidence of suspected lymph node involvement at the time of diagnosis was 41%. In the group of patients with elective lymph node dissection the incidence of metastases on definitive histopathology was 71.8%.

Conclusion: Extensive surgery, TT with dissection of central and lower jugular lymph nodes for frozen-section histology, in PTC enables diagnosis of nonpalpable lymph node metastases, precise surgical staging of disease and possible cure in patients with PTC. According to our data, this approach decreases the relapse rate in PTC.

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Thyroid cancer associated with Hashimoto thyroiditis

G. Horvatić Herceg[1], H. Tomić Brzac[1], I. Bračić[1], D. Herceg[2], S. Kusačić-Kuna[1], D. Dodig[1]. [1] *Clinical Department of Nuclear Medicine and Radiation Protection;* [2] *Clinic of Pathophysiology, University Hospital Rebro, Zagreb, Croatia*

The increased incidence of thyroid carcinoma (TC) in patients with Hashimoto's thyroiditis (HT) is well established in the literature, but the previous investigations were based mainly on pathohystologycal findings and only scintigraphic "cold" nodules were suspected as possible TC.

In our study ultrasound (US) and US guided fine needle aspiration biopsy (FNAB) were performed.

HT was diagnosed in 945 patients (pts) and in 36 of them TC associated with HT was found. TC appeared in 30 cases as hypoechogenic nodule, in 4 cases as isoechogenic, in 1 pt as cystic nodule and in 1 as calcified nodule. The size of carcinoma was <1 cm in diameter in 16 cases, 1–2 cm in 11 and >2 cm in 9 cases. Intraglandular dissemination and/or neck lymph nodes metastases were present in 19% of pts, and in the case of small carcinomas (<1 cm) in 37% of pts. All pts with TC underwent total thyroidectomy because of cytological finding. Papillary carcinoma amounted to 32 cases, follicular to 3 and medullary to 1 case. In all cases HT was confirmed hystologically and pts with perineoplastic and nonspecific thyroiditis were excluded.

Conclusions: 1.) We recommend careful US follow-up examinations of pts with HT. 2.) US-guided FNAB has to be performed in all patients with nodular form of HT (especially if the nodules are echographycally displayed as hypoechogenic). 3.) Small nodules (<1 cm) must not be neglected because they also tend to metastasize locally.

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Fine-needle aspiration cytology and frozen-section examination in pre- and intraoperative diagnosis of thyroid cancer

F. Lumachi[1], S. Borsato[2], S. Basso[1], F. Marino[3], M. Montesco[3], D. D'Amico[1], G. Favia[1]. [1] *Endocrine Surgery Unit, Department of Surg & Gastroent Sciences;* [2] *Section of Cytopathology, Department of Pathology;* [3] *Department of Pathology, University of Padua, School of Medicine, 35128 Padova, Italy*

Introduction: In contrast to thyroid nodules thyroid cancer is a rare condition which, in any case, requires an early diagnosis and treatment. In patients with nontoxic solitary thyroid nodules (NSTN) both fine-needle aspiration cytology (FNAC) and intraoperative frozen-section examination (IFSE) are usually requested for the adequate surgical planning. The aim of this study