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Peptide receptor radionuclide therapy (PRRT) with [IN-111-DTPA^0]octreotide (In-111-OC) in rats bearing the pancreatic somatostatin receptor (SSR) positive tumor CA20948

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Purpose: Lesions containing SSR in rats and in man can be visualized in vivo using In-111-OC. This radioligand is internalised via the SSR and In-111 has a long tumoral residence time, e.g. >700 h in humans. PRRT with high doses of In-111-OC was investigated in SSR-positive tumor-bearing rats.

Methods: Exp 1: CA20948 cells were injected into the portal vein on day 0, followed by 370 MBq In-111-OC (0.5 mg) per rat on day 1 and 8. Control rats received 0.5 mg only "cold" DTPA-Octreotide (OC). In Exp 2 the interaction of SSR and radioligand was blocked by 1 mg octreotide (octr) sc 30 min prior to the radioligand. The effect of 1 mg octr alone was also investigated. The rats were sacrificed on day 18 (Exp 1) or 21, and tumor colonies in the liver counted. Exp 3 was done as Exp 1 using SSR negative CC531 colon carcinoma cells.

Results are given in the table.

Conclusion: Peptide receptor radionuclide therapy with [In-111-DTPA^0]octreotide is effective and SSR-mediated.

Exp	Tumor colonies in liver				No rats
	0	1–20	21–100	>100	
1 OC	–	2	2	2	6*
In-111-OC	4	2	–	–	6
2 octr	–	–	–	6	6*
In-111-OC + octr	–	4	1	–	5*
In-111-OC	3	3	–	–	6
3 OC	–	–	3	3	6
In-111-OC	–	–	2	4	6

*: $p < 0.01$ vs In-111-OC; Mann-Whitney u-test.

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Somatostatin receptor scintigraphy (SSRS) in GEP-tumors

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Purpose and Methods: Many human neuroendocrine tumors express somatostatin receptors and can be visualized in vivo with SSRS. A blinded, cost-effectiveness study was performed comparing SSRS and conventional imaging techniques as applied in the routine setting of the localization of GEP-tumours.

Results: Carcinoids: Calculating sensitivities for conventional imaging and SSRS, based on the total number of lesions visualised by any technique, 92% of lesions in 96% of patients were demonstrated with SSRS. Comparable percentages were found by others, who also report additional lesions in about a third of patients. The cost-effectiveness study, combining only SSRS with chest X-ray and upper abdominal ultrasound, led to the detection of lesions in all patients in whom with any means they could be demonstrated. The cost of this imaging strategy was higher than that of conventional imaging only. The benefits, however, were the detection of at least one lesion in 15% of patients in whom with conventional imaging only no abnormalities were found and a doubling of the number of lesions. Gastrinomas: SSRS demonstrated lesions in 11/12 (92%) patients. Previously unrecognized sites were found in 5 of 12 patients (42%). The combination of SSRS and CT scanning of the upper abdomen had the highest sensitivity in patients with gastrinomas. The relatively high cost is outweighed by demonstrating a resectable tumor. Insulinomas: SSRS demonstrated tumour localizations in 10/24 (42%) patients. The highest yield against the lowest cost is obtained if SSRS is only performed if CT scanning fails to demonstrate the tumor. Pheochromocytomas: 13 of 15 (87%) pheochromocytomas were somatostatin receptor positive in vivo. Discrepancies between SSRS and MIBG scintigraphy in the staging of malignant pheochromocytomas have been observed. Further studies are required.

Conclusion: SSRS is the first localization technique for GEP-tumours, except for insulinomas. **Future:** Treatment with In-111 and Y-90 coupled somatostatin analogues has been initiated and may prove valuable in inoperable patients with somatostatin receptor positive tumors.

1230 ORAL

Peptide receptor therapy with ^{111}IN-DTPA-octreotide (OC)

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Purpose: In a phase 1 study, 20 end-stage patients with mainly neuroendocrine tumours were investigated. The emission of Auger and conversion electrons by OC is used to induce an anti-proliferative effect.

Methods: The typical doses per administration were 6–7 GBq ^{111}In labeled to 40 μg DTPA-octreotide, given with 2 to 3 weekly intervals and a maximum of 12 administrations.

Results: No major side effects were noticed in the first treated patient after a cumulative dose of 25 GBq and a follow-up interval of 2 years, which is so far the longest follow up period. In the other patients no major side-effects were observed as well, although in 2 patients a transient thrombocytopenia and in most patients a decrease in lymphocyte-subsets without clinical symptoms have been found. No clinically relevant changes in kidney function were observed. Impressive effects on the clinical condition and on hormone or tumour marker production were observed, though in some patients temporary because of end-stage disease. Also, anti-proliferative effects have been noticed. Of all 20 patients with progressive disease, i.e. unequivocal increase in tumour-volume according to CT or MRI for six months prior to the start of OC therapy, in 12 patients this treatment resulted in either stable disease or actual tumour shrinkage up to 65%.

Conclusions: So far a response to treatment with OC, based on antiproliferative effects and a lowering of tumour markers in serum and/or urine, has been obtained if 1. the cumulative therapeutic dose of OC was at least about 450 mCi (17 GBq) and 2. tumour uptake was at least grade 2. **Future:** Radiotherapeutic use of radionuclides with higher energies of β-particles, e.g. ^{90}Y, coupled to DOTA-chelated Tyr-3-Octreotide, will lead to higher radiation doses in a larger part of the tumour because of their more appropriate tissue-penetration. Thus, tumours with an inhomogeneous distribution of peptide receptors may then respond favourably.

1231 ORAL

Telomerase activity in benign and malignant human thyroid disorders

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Introduction: Accumulating evidence has indicated that telomerase is stringently repressed in normal human somatic tissues but reactivated in cancers and immortal cells, suggesting that activation of telomerase activity may play a role in carcinogenesis. In this work, telomerase activities in benign and malignant human thyroid disorders were evaluated.

Methods: Telomerase activities were examined in 62 frozen samples obtained from patients with benign and malignant thyroid nodules. Samples diagnosed for specific pathology were confirmed histologically. Telomerase activity assay was performed with a PCR-based telomeric repeat amplification protocol (Science 266: 2011, 1994).

Results: Telomerase activity was detectable in 2 of 14 (14%) nodular hyperplasia, 4 of 14 (29%) adenoma, 12 of 23 (52%) papillary carcinoma and 10 of 11 (91%) follicular carcinoma tissues. Most of the papillary and follicular cancers with advanced stage (stage III or IV) were positive for telomerase activity. On the other hand, cancers shown negative for telomerase activity were mostly in early stage (stage I). There is no significant correlation of telomerase activity with the level of thyroid globulin or with patient age.

Conclusion: The presence of telomerase activity is correlated with the prognosis of malignant thyroid disorders. These results suggest that telomerase activity may play a role during thyroid tissue carcinogenesis, and may serve as an aid in the diagnosis of malignant thyroid disorder.

1232 ORAL

The value of scintigraphy for diagnosis in differentiated thyroid cancer is questionable

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There is a continuing controversy about the value of scintigraphy for preop-

erative diagnosis of differentiated thyroid cancer.

Methods: We analyzed 119 patients operated for thyroid carcinomas from 1987–1996 and 217 patients operated for benign diseases of the thyroid from 1994–1996. We investigated the value of scintigraphy for operative decision making in both groups. Preoperative standard diagnostics enclosed clinical evaluation, thyroglobulin, ultrasound, scintigraphy, fine-needle aspiration biopsy.

Results: Preoperative diagnosis of thyroid cancer was correct in 47/119 patients. Another 17 malignomas were detected after intraoperative frozen section. Nearly half of the patients had a definite diagnosis only after postoperative histologic investigations (n = 55).

Among cancer patients thyroglobulin measurement had a sensitivity of 77% (44/57 pts.) compared to 80% and 73% sensitivity for ultrasound and scintigraphy, respectively. The specifity of these methods was 50% for thyroglobulin compared to 82% and 62% for ultrasound and scintigraphy. Fine-needle biopsy was performed in 55 cancer patients giving a correct preoperative diagnosis in 40 pts. (cancer in 21 pts., suspected cancer in 19 pts.) (sensitivity 73%, specifity 96%).

Conclusions: Ultrasound and fine-needle biopsy proved to be essentially for definite operative decision making. Scintigraphy was uneffective giving a very low specifity.

1233 ORAL

Well differentiated thyroid cancer: Analysis of survival for 299 operated patients

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Aim of the Study: 1) Evaluation of the validity of the initial surgery with regard to the initial Prognostic Index (PI) (as defined by the E.O.R.T.C.) – 2) Evaluation of the occurrence of local, regional or distant metastases – 3) Impact on survival.

Material and Method: 299 Patients (PTS) (86 M; 213 F) consecutively operated from 1955 to 1995 in our Institution for well differentiated thyroid cancer with or without adjuvant I_{131} all placed on supressive hormonal treatment. Histology of primary: 220 papillary, 31 follicular, 48 moderately differenciated follicular cancer. Mean age 46.3 years (7 to 81 yrs). 28 PTS had various surgeries before being referred, definitive surgery accomplished = 121 total thyroidectomies (TT), 38 subtotal bilateral lobectomies, 38 total unilateral and subtotal contralateral lobectomies, 96 total unilateral lobectomies, 2 isthmusectomies and 4 biopsies. Tracheotomy mandatory for 13 PTS. Recurrent nerve lymph node dissection: 78 PTS, lateral neck dissection: 90 PTS. I_{131} was given to 138 PTS (122 for thyroid tissue ablation, 11 for residual thyroid tumor, 5 for distant metastases only). 35 PTS: additional external radiation (either for residual thyroid tumor, or for invaded lymph nodes or for "shave-excision").

Results: After a median follow-up of 15 yrs (12 to 488 months), 224 PTS are alive (NED) among 274 PTS for whom neither distant metastases at presentation (n = 11) nor residual tumor was left after the operation (n = 14). The PI inferior or equal to 50 (n = 146 PTS) predicts a 10 yrs Survival of 98.5% versus 75.6% for 128 PTS with PI superior to 50 ($p < 0.0001$). S 10 yrs of 63 PTS after unilateral lobectomy with PI inferior or equal to 50 is 97% (n = 63; 2 deaths) whereas S 10 yrs of 53 PTS with PI superior to 50 treated with TT is 65% (n = 53; 22 deaths).

1234 ORAL

Prophylactic thyroidectomy in MEN IIA gene carriers – An intervention with a justifiable morbidity?

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Background: The fate of MEN IIA patients is determined by the medullary thyroid carcinoma. Molecular-genetic diagnostics enable early recognition of the gene carrier and prophylactic thyroidectomy in childhood. Every prophylactic surgical intervention must be critically examined regarding the risks involved for the patient. We have analyzed our prophylactically operated children and adolescents under this aspect.

Methods: In the past 2 years, 8 children and adolescents (4 male/4 female) with MEN IIA underwent prophylactic thyroidectomy and central lymphadenectomy, followed by mandatory exposure of the recurrent laryngeal nerve and parathyroid.

Results: In 4 patients (age: 4–9 years), C-cell hyperplasia was histologically detected as a precursor of the carcinoma. Three patients (age: 9–24 years) had a T1 carcinoma without lymph node metastases. A 9-year-old boy had a T1 carcinoma with an ipsilateral lymph node metastasis. There were no wound healing disturbances or bleedings. Postoperative recurrence weakness (1 case) or hypocalcemia (3 cases) regressed completely.

Conclusion: Early prophylactic thyroidectomy in MEN IIA patients is oncologically justifiable and should be performed in special centers with an acceptably low morbidity for the children and adolescents concerned.

1235 PUBLICATION

A phase II study of interferon alpha-2a (IFNα) and modulated 5-fluorouracil (5-FU) in patients (pts) with advanced neuroendocrine tumours (NET)

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Background: Both 5FU and IFNa have shown modest single agent activity in pts with NET, with biochemical responses much more common than objective responses. The combination of 5FU and IFNa has shown synergy in tumour models, and activity in gastrointestinal malignancies.

Methods: 15 pts with advanced NET (12 carcinoid, 2 islet cell, 1 phaeo.) of whom 3 were non-secretors, were treated with leucovorin 200 mg/m2 i.v. infusion over 2 hours, then 5FU 400 mg/m2 i.v. bolus followed by 400 mg/m2 i.v. infusion over 22 hours all repeated on day 2; IFNa was given at 6 × 106 IU s.c. every 48 hours throughout. Treatment was given every 2 weeks for up to 12 cycles. In case of stable disease (SD) or partial response (PR), IFNa was continued until disease progression (PD). All pts were chemotherapy naive; one pt had prior treatment with 131I-metaiodobenzylguanidine.

Results: Patients received a median of 5 courses (range 1–12). Two pts achieved a PR (13%; 95% confidence interval 2–40%), of 3 and 4 months duration. Five pts achieved SD (33%), for a median of 8 months (range, 4–22 months). Both pts who achieved PR and 3/5 with SD had a >50% marker reduction (5-HIAA, VMA, VIP, Gastrin) correlating with symptomatic response. Four pts had PD. Another 4 were not assessable for response due to early toxicity requiring cessation of treatment. Two had grade III–IV diarrhoea and 2 grade IV neutropenia requiring i.v. antibiotics.

Conclusions: These results suggest no clear advantage for the combination of 5FU and IFNa over the individual agents; the combination *may* also result in increased toxicity

1236 PUBLICATION

Combined therapy for advanced thymoma

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Thymoma (THY) is a locally invasive mediastinal tumor frequently associated to several paraneoplastic syndromes, most notably miastenia gravis. Late local relapses are frequent. Treatment of advanced THY (Masaoka stages III–IV) with local therapy alone has a high incidence of relapse. There are few studies on multimodal therapy in this setting. From 1986 to 1995, 9 cases of THY have been diagnosed at our institution. Median age was 53 years (28–69). Sex (male/female): 5/4. In addition to local symptoms, 2 patients (pts) had miasthenia gravis and 2 had red cell aplasia (pure in 1, associated to thrombocytopenia in 1). Stage (Masaoka): III in 7 pts, IVA (pleural metastases) in 1 and IVB in 1 (single lung metastasis). Two pts were initially treated with surgical resection. The other 5 were treated with cisplatin-containing chemotherapy: CAP (2), PBV (2), PIA (1). All 5 had a partial response (PR), but 1 died of neutropenic sepsis at 2 months. The remaining 6 pts plus 1 pt with mediastinal relapse after surgery and 1 previously untreated pt received external radiotherapy (45–60 Gy). Response after radiotherapy was complete in 4 pts and PR in 4. With median follow-up of 71 months, 4 pts had a local progression at 30 months (24–36). One is alive with disease at 25 months and 3 died with progressive disease at 24, 26 and 96 months from initial therapy. This last pt achieved successive PRs to 3 regimens of chemotherapy and survived for 60 months after progression. Four pts remain alive and progression-free at 12, 61, 81 and 86 months. Survival for all pts is 60% at 5 years. Pts with advanced THY can have long progression-free survival if adequate local control is achieved. Since advanced THY is very chemosensitive, combined locorregional and systemic front-line therapy is a reasonable approach, in the absence of conclusive evidence from randomized trials, given the rarity of this tumor.