Intervention model for cancer control in a low-income African area

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Background: Cancer outcome is an emergency in low-income areas (LIAs) such as Tanzania, where incidence is 84 and 91 per 100,000 males and females, respectively. Prior to 2008, an Oncology Department (OD) did not exist at Bugando Medical Center (BMC), Mwanza, Tanzania (catchment area of 14 million people).

Methods: Thanks to an agreement between BMC, Association Tison, IRST, and Istituto Oncologico Romagnolo, a Pathology Laboratory and an OD were instituted in 2000 and 2008, respectively. The oncology team comprises a multidisciplinary staff of 13, including 1 physician and 3 nurses who received cancer training at IRST. Volunteer Italian oncologists provide support for the Tanzanian team each month.

Results: Between Jan 2009 and Dec 2010, 1610 patients were admitted to BMC OD, of whom 511 were children and 1099 adults (670, 61% females; 429, 39% males). The majority of children (70%) had Burkitt's lymphoma, 20% retinoblastoma and the remaining, acute leukemias, Wilm's and brain tumors.The highest rate of cancer in adults was cervical cancer in females (32%) and hepatocarcinoma (HCC) in males (30%). Out of 562 women screened for breast and cervical cancer, only 3% had stage I breast cancer, treated with curative intent. Among patients screened for cervical cancer, 18% showed alterations at colposcopy, and biopsy confirmed cancer. One third of these were inoperable locally advanced cervical tumors.

Conclusions: Cancer epidemiological patterns in Tanzania differ from those of high-income areas (HIAs) due to the high prevalence of infection-related cancers. Several challenges exist: inadequate or poorly accessible diagnostics; drug availability and cost; patients lost to follow up; lack of palliative care culture; and bureaucracy. This transnational collaboration aims to improve the quality of oncology care and to foster no-profit trials on tumors with a low incidence in HIAs, but with greater relevance in LIAs.

No. patients (%) admitted to the BMC OD

	Cervix	HCC	Breast	Kaposi's Sarcoma	Esophagus	Hodgkin's Lymphoma	Prostate	Ovary	Others	Total
Males	-	129 (30)	-	64 (15)	77 (18)	38 (9)	73 (17)	-	48 (11)	429 (39)
Females	214 (32)	-	141 (21)	47 (7)	34 (5)	67 (10)	-	20 (3)	147 (22)	670 (61)
All adults	214 (32)	129 (30)	141 (21)	111 (10)	111 (10)	105 (9)	73 (7)	20 (2)	195 (18)	1099

Survival prediction for terminally ill cancer patients: revision of palliative prognostic score with incorporation of delirium

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Background
The validated Palliative Prognostic (PaP) score predicts survival in terminally-ill cancer patients and is calculated on the basis of dyspnea, anorexia, Karnofsky Performance Status, clinical prediction of survival, total white blood count and lymphocyte rate. The impact of delirium is known but was not incorporated in the original PaP score. Our aim was to incorporate information on delirium into this score.

Methods
The study was based on a retrospective series of 361 terminally-ill cancer patients. The main endpoint was overall survival. We used the 'validation by calibration' approach proposed by van Houwelingen et al. and later adapted by Miceli et al. to obtain a score revision with inclusion of a new variable. A new model is fitted including the original score and the new variable as covariates; the model parameter estimates are then used to calculate the partial score for the new variable and the revised cutoffs to define the prognostic categories.

Results
The prognostic contribution of delirium was confirmed as statistically significant ($p<0.001$) and the variable was incorporated into the PaP score (D-PaP score) accordingly. With such a revision, 30-day survival in the three risk groups (A>70%, B 30-70%, C<30%) was 83% (95% Confidence Interval CI 77-90), 50% (95% CI 42-58) and 9% (95% CI 3-15) vs 87% (95% CI 80-93), 51% (95% CI 44-59) and 16% (95% CI 8-24) obtained using the original PaP score. PaP and D-PaP score classifications were in accordance in 292 patients (80.9%). Seventeen (4.7%) patients were switched to a group with a less favorable prognosis and 52 (14.4%) were switched to a more favorable prognostic group. The frequency of patients with delirium, 14 (10.1%) and 37 (25.9%) in groups A and B, sharply increased to 48 (60.8%) in group C. The overall prognostic performance of the revised score was better than that obtained with the original one.

Conclusions
The model validation and revision was carried out by modifying the cut-off values used for prognostic grouping without affecting the partial scores of the original PaP score. The revision improved the performance of the original PaP score whilst maintaining its key feature of simplicity.

Neutropenia with adjuvant epirubicin-CMF confers improved survival in patients with node-negative or 1–3 node-positive rapidly proliferating breast cancer.

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Abstract Text:

Background: Patients who experience at least some degree of neutropenia whilst receiving adjuvant chemotherapy for breast cancer show improved survival. Tumor proliferation is a prognostic marker in breast cancer. We therefore hypothesized that patients with rapidly proliferating breast cancer and evidence of neutropenia whilst on adjuvant chemotherapy would have a better survival than that of similar patients in whom there was no evidence of myelotoxicity. **Methods:** We reviewed the case notes of 173 women treated in Wide Area of Romagna cancer centers with epirubicin followed by the intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) regimen or the inverse sequence for rapidly proliferating breast cancer, defined by thymidine labeling index (TLI) >3%, to identify patient- and treatment-related factors influencing outcome. **Results**: The actuarial 5-year overall survival for these women was 94%, with the anticipated poorer outcome for those with higher TLI (≥10% vs <10%, P=0.032). There was no evidence that ER-negative tumors, HER-2 positive disease or older age at presentation resulted in poorer survival. Of note, the absolute survival advantage was confined to the 47% of patients who had grade 3/4 neutropenia (P<0.001) with respect to those with grade 0-2 neutropenia (P=0.268). **Conclusions:** Our results suggest that neutropenia has a greater influence on outcome than age and tumor biological factors in patients with rapidly proliferating breast cancer.

Dendritic cell (DC) vaccination with low dose temozolomide Phase I/II trial in melanoma patients: Preliminary data on peripheral blood regulatory t-cells (Treg) and DC-TEM8 expression modulations.

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Abstract Text:

Background: Cytolytic T lymphocytes (CTL) able to kill tumor cells are efficiently induced by Dendritic Cells (DC); however, immunosuppressive factors, as CD4+CD25+FoxP3+ T lymphocytes (T-reg) and TEM8 expression by DC, hamper efficient activation. After our experience of a vaccination trial using autologous mature DC (mDC) pulsed with autologous tumor lysate (ATL) and Keyhole Limpet Hemocyanin (KLH), in 2007 we started a phase I/II study with low-doses temozolomide (ldTMZ, given by Schering Plough Italy) before the vaccine in metastatic melanoma patients. **Methods:** TMZ 75mg/m2/day (maximum total dose 100mg/day) for 14 days (-14 to -1), DC Vaccination (day 0), and IL-2 3MUI/day s.c (days 2-5) q every 2 weeks for the first 4 vaccine and then monthly. Clinical and radiological evaluation as well as Delayed-type hypersensitivity (DTH) test for in vivo immunomonitoring were performed at basal and every 4 vaccinations. Circulating T-reg were evaluated at day -14, 0 and after IL-2. TEM8 expression in mDC (TEM8 mRNA ratio mDC vs immature DC) was investigated in 5 non progressing patients (NP) and in 7 progressing patients (PD) by QRT-PCR. **Results:** Up to september 2010, 17 patients were treated (5 females and 12 males, median age 57 years). Out of 15 evaluable patients 1 showed partial response (PR) of 6 months, 6 stable disease (SD) of 4,4,4,9,9,10 months and 8 progressed (PD), without major toxicities. All responders had positive DTH test, although weak in 1 patient with SD and in 3 patients with PD. TEM8 mRNA levels increased after iDC maturation, but no significant difference was found in mDC TEM8 expression mean fluorescence intensity between NP and PD. The absolute number of Treg (evaluated in 12 patients) decreased after TMZ treatment in 4 of the 6 PD patients and in all NP patients; however, after IL-2 administration, all patients except 4 of the 7 NP showed a rebound peak of Treg. **Conclusions:** These preliminary data suggest that ldTMZ may down-modulate T-reg population. Further investigations are needed to understand the role of T-reg and their relatively low growth after IL-2 administrations in NP patients.

Process and outcome indicators for evaluation of surgical activity in a high-risk gastric cancer area.

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Abstract Text:

Background: Numerous studies have been published on the relationship between hospital volume and quality of results in oncologic surgery. However, the relative importance of hospital volume in various surgical procedures is open to discussion because of study design heterogeneity. Differences in patients and provider characteristics can make volume appear to have a greater influence on outcome than it actually does. We aimed to identify appropriate process and outcome indicators to detect high quality providers and to assess the real role of hospital volume in clinical outcome in gastric cancer surgery procedures. **Methods:** We retrospectively collected data from 1680 gastric cancer patients who underwent total/subtotal gastrectomy in public/private hospitals in Romagna (population of about 1 million, 7 general hospitals and 8 private clinics, all with surgery units) from 2004 to 2008. Data on duration of hospitalization, patient characteristics, comorbidities, diagnosis, surgical intervention, lymph nodes removed and lymph node stations dissected were collected from electronic hospital records. Hospital performance indicators were hospital procedure volume and procedure volume for each surgical unit and for each surgeon. Provider factors were staffing levels and hospital facilities. Main clinical outcome measures were operative mortality, 30-day mortality, overall survival and complications. **Results:** 88.3% of the surgical activity was concentrated in general hospitals. More than 80% of patients were referred to their nearest general hospital. 30-day mortality rate was 7.26% and was inversely correlated with hospital volume. The median duration of hospitalization varied between 11 and 24 days and was lower in hospitals with a higher number of gastric cancer patients. **Conclusions:** Our results did not identify a reference center for gastric cancer surgery in Romagna but did highlight the need to improve the quality of surgical care, including increased health regionalization and development of common protocols for surgery procedures. A more complete analysis taking into account patient characteristics and hospital facilities is ongoing. Partially funded by Istituto Oncologico Romagnolo.

Thyroid metastases from clear cell renal cell carcinoma: A case report.

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Abstract Text:

Background: Renal cell carcinoma can metastasize to unusual sites such as the thyroid gland. Such cases typically present with a unilateral painless cold nodule at scintiscan, hypoechogenic at ultrasonography, with final diagnosis made by fine-needle aspiration. **Methods**: An 87-year-old woman with clear cell renal cell carcinoma was treated by radical nefrectomy in April 2003. She relapsed in 2009 in the abdomen and underwent resection of the large, symptomatic metastasis. Around the same time bilateral lung lesions appeared. The patient was subsequently treated with sunitinib 50 mg daily in cycles of 4 weeks with a two-week interval. The dose was reduced to 37.5 mg because of bone marrow toxicity. After 17 months of treatment the lung metastases were stable but bilateral thyroid nodules were detected. **Results**: Thyroid function tests were normal. Ultrasound-guided biopsy found atypical cell aggregates with clear cytoplasm and positivity for CD10 and vimentin, compatible with clear cell renal cell carcinoma. The patient began treatment with everolimus in January 2011. **Conclusions:** Although thyroid metastases from clear cell renal cell carcinoma are extremely rare and generally only appear, along with other extra-thyroid metastases, many years after the primary diagnosis, they must be taken into consideration in patients with a long history of renal carcinoma.

Accuracy in targeted therapy prescription: An observational retrospective study.

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Abstract Text:

Background: Targeted therapy has led to a greater need for detailed information on the disease, and several biological markers have become crucial for the identification of the best treatment option. Although international guidelines provide evidence-based recommendations and national and local laws regulate the prescription process, physicians are often faced with situations that can lead to a not fully appropriate use of drugs in daily clinical practice. **Methods:** An observational retrospective study on 341 cancer patients at different treatment stages was carried out at the Cancer Institute of Romagna (I.R.S.T.) from January to June 2010. A panel of innovative drugs utilized for the therapy of four tumor types was evaluated to assess the accuracy of the drug prescription process (Table). Major international guidelines were reviewed to identify the biological markers recommended for evaluation in each disease, and Italian and Regional reference documents pertaining to treatment indications were consulted to identify the markers whose determination was mandatory. **Results:** Erb-2 was investigated in all the breast cancer patients and K-Ras was evaluated in 32 (72.2%) of the 44 advanced/metastatic colon cancer patients. A small number of patients eligible for treatment with a drug indicated for his/her disease did not receive the drug. In NSCLC, although the use of Erlotinib did not require biological marker evaluation, EGF-R determination was performed in 23 (31%) of the 74 advanced/metastatic patients. **Conclusions:** Our study showed that the drugs evaluated were appropriately prescribed in all cases. EGF-R evaluation would still not appear to be closely correlated with the use of Erlotinib in NSCLC. Similar analyses are planned and outcome indicators are undergoing evaluation in other centers to compare the degree of drug prescription compliance among the hospitals of the Wide Area of Romagna network. Partially funded by Novartis SpA.

Disease	Marker	Drug	No. markers investigated/no. pts	Positive marker (no. pts)	No. pts treated
Breast cancer	Erb-2 amplif.	Trastuzumab	195/195	58	55
Colon cancer	K-Ras w/t	Cetuximab	32/58	20	13
GIST	C-Kit amplif.	Imatinib	6/6	6	6
NSCLC	EGF-R amplif.	Erlotinib	23/84	5	19

Response of brain metastases from non small cell lung cancer to first-line pemetrexed-based chemotherapy: A single center experience.

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Abstract Text:

Background: Non Small Cell Lung Cancer (NSCLC) accounts for almost 80% of all lung malignancies, and 40% of these patients go on to develop brain metastases (BM). Furthermore, there are no grade I recommendations for the management of multiple BM. The most widely used treatment is whole-brain radiation therapy (WBRT). Current data on pemetrexed suggest that it is active against BM. This drug was recently made available in Italy for front-line treatment of non-squamous NSCLC. **Methods**: In 2010 we observed 8 patients with central nervous system metastases from non-squamous NSCLC at diagnosis. Patients were treated with first-line cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 for a minimum of 3 cycles up to a maximum of 6 cycles in the absence of progressive disease (PD). **Results**: With regard to brain lesions, 5 patients had partial response (62.5%), 1 had complete response (12.5%), 1 showed stable disease (12.5%) and 1 had PD (12.5%). Only two patients were treated with concomitant WBRT, showing a partial response that continued during treatment and up to the final evaluation. **Conclusions**: Our data, although based on a relatively small case series, seem to confirm the activity of pemetrexed-based therapy against BM. If confirmed in a larger sample of patients, these results could modify the management of multiple BM by delaying radiotherapy in asymptomatic patients until PD occurs.

Mini-gene profiling for the prediction of bone metastases in breast cancer patients.

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Abstract Text:

Background: The process of bone metastasization includes numerous steps such as proliferation, invasion and adhesion, involving molecules, growth factors, chemochines and their receptors that confer the bone-like phenotype. Thus, only cancer cells with specific features will be able to reach and colonize bone tissue. The early prediction of relapse in this site could be clinically useful to select patients for a tailored therapy based on bone specific drugs such as bisphosphonates or RANK-L inhibitors . **Methods:** The study retrospectively evaluated the levels of TFF1, DKK1, IBSP, HPSE, SPP1, Agr2, SPARC, CTGF, COMP, FST, and RANK transcripts by Quantitative Real-Time PCR in the fresh frozen breast cancer samples of 40 patients to predict cancer relapse and the sites of relapse. Fifteen patients had no evidence of disease (NEDP), 15 had bone metastases (BMP), and 10 had visceral metastases (VMP). The predictive accuracy of each marker was calculated using Receiver Operating Characteristic (ROC) curves. **Results:** The median values of each marker were calculated for each subgroup: TFF1 median values were about 7 times higher in BMP than in control groups (p=0.05); COMP and HPSE median values were about twice as high in BMP compared to both NEDP and VMP. The area under the curve (AUC) was 0.73 for TFF1, and 0.62 for HPSE and COMP. Considering markers as dichotomous variables, TFF1 expression reached 67% in BMP compared to 21% and 20 % in NEDP and VMP, respectively. TFF1 was also analyzed in combination with other markers and, considering positivity of at least one marker among TFF1, DKK1, and IBSP, an expression level of 80% was reached for the BMP group, whilst the same low expression level was maintained in both control groups (p=0.041). **Conclusions:** Our preliminary results show that the analysis of 3 gene expression markers, TFF1, DKK1 and IBSP, in primary breast tumors could be useful to predict the patients who will relapse to bone tissue. However, a larger case series should be performed to understand the role of these markers in the selection of patients eligible for adjuvant preventive bone specific therapy.

Sequential treatment strategy for metastatic colorectal cancer: A phase III study of chemotherapy (CT) with or without bevacizumab (Bev) as first-line therapy followed by two phase III studies of CT alone or CT+bev with or without cetuximab (Cetux) as second-line therapy (ITACa Study IRST 153 01).

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Abstract Text:

Background: The commercialization of two monoclonal antibodies, bevacizumab (Bev) and cetuximab (Cetux) raises important questions about their use in the first- and second-line treatment of metastatic colorectal cancer. At present, their role in clinical practice is not well defined, especially in terms of timing of administration and possible side-effects compared to chemotherapy (CT) alone. **Methods:** Patients eligible for first-line treatment will be randomized to either treatment arm A: CT (FOLFOX or FOLFIRI at the physician's discretion) + Bev or arm B: CT alone. The primary objective of this part of the study is to compare progression-free survival (PFS) in treatment arms. Upon progression, patients from arm A with Kras wild-type tumors will be randomized to arm C (the other CT schedule alone) or arm D (the other CT schedule + Cetux). Arm B patients with wild-type Kras will be randomized to arm E (the other CT + Bev) or arm F (the other CT+ Bev + Cetux). The superiority hypothesis regarding the use of Bev in first-line therapy requires 310 events (progressions) in a total of 350 patients to detect an absolute increase in PFS of 3 months, corresponding to a 27% relative reduction in the progression rate, with a 2-sided 5% significance level and an 80% power. It is assumed that about 75 patients will be included in each of the second-line studies. PFS as primary objective is an amendment currently under evaluation of the Ethical Committee. The objective response rates, OS and safety are secondary endpoints. The identification and evaluation of the role of tumor markers in predicting treatment response is one of the sub studies. **Results:** This independent study will be funded by the Italian Ministry of Health. At the end of December 2010, 24 centers had received Ethics Committee approval, and 23 are currently recruiting patients. To date a total of 267 patients have been randomized onto the first-line study. **Conclusions:** We plan to close recruitment in December 2011 and perform the final analysis in September 2012.