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Improving cancer outcomes by promoting medicines adherence

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Medicines non-adherence has been flagged up as a health problem of crisis proportions that can result in disease progression, reduced quality of life and even death. Despite its high human and financial cost this problem has been overlooked as a serious public health issue. Non-adherence is seen across a range of cancer scenarios including adjuvant endocrine therapy (both tamoxifen and aromatase inhibitors), supportive care (eg. anti-biotics) and treatment with oral targeted therapies such as imatinib. The true extent of non-adherence to oral cancer medicines is unknown – estimated rates vary across diseases, drug regimens and age groups. Older people, adolescents and those with chronic diseases requiring long-term or life-long treatment are thought to be at greatest risk for non-adherence. Persistence with treatment is also a problem with a number of studies showing that persistence rates fall considerably after 12 months of treatment. Experts in the field argue that non-adherence should always be considered if a patient does not respond to therapy, however, lack of awareness of the problem often means that this potential diagnosis is overlooked. The growing shift towards oral cancer therapies offers patients benefits in terms of convenience; however, it also means that in coming years non-adherence may emerge as a problem of huge magnitude in the oncology setting.
Medicines non-adherence is a complex, multi-faceted problem that is influenced by behavioural, social, economic and medical factors and therefore difficult to tackle effectively. The complexity of a drug's administration schedule, side-effect profile and treatment length can all have a profound impact on a patient's ability or willingness to comply with treatment. Some simple strategies can help promote adherence – the provision of easy-to-understand information about medicines is a key first step. Reminder devices can prove useful particularly when patients start out on a new treatment. If side effects are managed patients will cope better with long-term treatment and careful monitoring of patients can help detect adherence problems early. A positive relationship and open communication between health professionals and patients is also important. From a policy perspective there is a need to give greater priority to medicines non-adherence and to start implementing strategies that may help reverse this ever-increasing problem. If we do not take steps to tackle non-adherence with oral cancer therapies today, there could be significant negative consequences for cancer outcomes tomorrow.

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Benefits of a healthy diet for cancer patients

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Background: Breast cancer (BC) is the most common malignancy in women and is their leading cause of death from cancer. In high-income countries the incidence of BC has increased steadily over the past decades, but BC mortality is declining, suggesting a benefit from early detection and more effective treatment. BC survivors are constantly increasing, and research investment for the identification of modifiable factors associated with BC recurrences is increasing too. Western lifestyle, characterized by low levels of physical activity and a diet rich in refined carbohydrates, animal fats and protein is associated with high prevalence of metabolic syndrome, insulin resistance and high serum levels of sex hormones and growth factors. All these factors are strongly related with BC risk and BC prognosis but are potentially modified through diet and lifestyle.
Methods: The present work summarizes the metabolic, hormonal and dietary correlates of increased risk of BC and BC recurrences.
Results: Obesity is associated with an increased risk of BC after menopause while no association or slightly reduced BC risk has been found before menopause. Preventing weight gain in adulthood, however, would decrease the overall burden of BC. Obesity has been shown to adversely affect prognosis in both pre and post-menopausal BC, after controlling for clinical and pathological prognostic factors. High serum levels of steroid sex hormones, and of bio-available insulin-like growth factor I (IGF-I) are associated with an increased risk of BC. Furthermore, insulin and markers of insulin resistance such as abdominal obesity, high blood glucose, high serum level of testosterone, and metabolic syndrome may effect both BC incidence and prognosis. Sedentary life-style is associated with increased BC risk, both before and after menopause. Women who practice regularly at least some physical activity decrease their BC risk by 30% or more and there is increasing evidence that physical activity may protect also against BC recurrences. The association between dietary fat intake and BC is an highly controversial topic in epidemiology. Results of the Women Initiative on Nutrition Study (WINS), a randomized dietary prevention trial, suggested a strong benefit of dietary fat reduction on relapse-free survival with the strongest protection for hormone receptor-negative BC. The Women's Healthy Eating and Living (WHEL) Study tested whether a dietary pattern high in vegetables, fruit, and fiber and low in fat might reduce BC relapses in women with early-stage BC. The primary analyses of the WHEL study did not demonstrate an event-free survival advantage in patients randomized in the dietary arm. This trial, however, was isocaloric and the intervention group did not loose weight.
Conclusions: The breafly reviewed factors are strongly related to diet and life-style and may be potentially modified. Our DIANA (DIet and Androgens) intervention trials demonstrated that a sustainable dietary modification aimed at lowering insulin levels, based on Mediterranean and macrobiotic dietary principles, can reduce body weight, metabolic syndrome, and the bioavailability of sex-hormones and growth factors. Together with other studies showing that Mediterranean diet can revert metabolic syndrome, these results suggest that dietary changes should be recommended for both BC prevention and treatment.

Special Session (Tue, 22 Sep, 17:00−18:00)
Specific issues in lung cancer management

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How to approach oligometastatic disease – is there a role for surgery?

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Patients with non-small cell lung cancer (NSCLC) are treated according to defined algorithms depending from the TNM stage. In presence of metastatic disease (stage IV) palliative treatment is usually recommended. However long term survivors or even cure was observed in selected patients with NSCLC who underwent surgery alone or in combination with other treatment despite distant metastases either to the lungs, the brain and the adrenal or other structures are present. These observations are confirmed in several published case series or a few phase II studies.
The question is, who are the individuals who may profit from resection of the primary site as well as the metastases and which other treatment modalities should be combined and in which timing. In general patients with metastatic disease from NSCLC have a poor prognosis. Precise imaging tools for staging such as positron emission tomography integrated in computer tomography (PET-CT), CT scan or MRI allow a precise description of the extend of the disease. Metastases are identified earlier and the number and location are diagnosed more accurate. Therefore it is not surprising that complete resection in combination with systemic therapy are considered as treatment options for well circumscribed disease. Currently we rely for decision making on images, histology and finally the TNM stage. In the future molecular markers may help to select patients for best therapy. The current literature on the role of surgery in oligometastatic disease reports outcome data from patients with metastatic cancer nodules in the lungs located either in the same lobe or different lobes, pleural metastasis and malignant pleural effusion and metastases to various organs mainly the brain or the adrenals.
Nodules in the same lobe of the primary lung cancer (satellite nodules) are considered to be T4 disease because of the better prognosis. If located in another lobe they are diagnosed as M1 disease. Several studies report a 5 year overall survival rate of 20−25% for surgically treated patients. Several questions remain unsolved such as to the extend of resection when the nodules are in different lobes (segmentectomy in combination with a lobectomy versus a pneumonectomy) and the role of adjuvant or neoadjuvant therapy.
Patients with malignant pleural effusion or pleural nodules without extra thoracic or extensive mediastinal lymph node disease were occasionally operated in a curative attempt either by pleurectomy or even pleuropneumonectomy. Despite some reports on individuals with long term survival the prognosis in general is poor and palliative treatment is recommended for most cases.
Extra thoracic metastases to the brain are observed in about 25% of patients with Stage IV NSCLC. Surgical resection or stereotactic radio surgical techniques are applied as complementary modalities. Complete resection of brain metastases together with the primary lung cancer in absence of mediastinal lymph node metastases may result in 5 year survival rate of 20−25%. The role of adjuvant chemotherapy and the role of whole-brain radiotherapy remains controversial but both modalities are applied in many centres.
Metastasis to the adrenal is a frequent site for metastasis of NSCLC as well. In absence of other tumor surgical resection preferentially by laparoscopic technique may be considered. The 5 year overall survival rate ranges from

10−23%. Prognosis may be positively influenced by a longer disease free interval of more than 6 months after initial lung resection.
Despite the lack of randomised studies as well as prospective phase II studies the current literature suggests that well selected patents with oligometastatic disease may profit from an individualised treatment including complete resection of the primary tumor as well as the metastases. Not only the indication for surgery is ill defined in the current literature also the role of adjuvant chemotherapy or radiotherapy is unclear despite it is often used in combination with surgery. Improvement in imaging modalities and minimal invasive staging techniques allow more reliably to define the macroscopic tumor extend.

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Which is the best treatment for non-small lung cancer patients with PS 2?

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Patients with performance status of 2 (PS 2) usually account for a small proportion of patients enrolled in trials of first-line treatment for advanced disease but represent a significantly higher proportion (up to 30–40%) when population-based surveys are conducted. As in other types of cancer, PS has a clear prognostic role in advanced NSCLC. Median overall survival of patients with PS2, whatever the treatment under investigation, is always substantially shorter than that of PS0 or PS1 patients, and rarely exceeds 5 months, with 1-year survival rates <20%, and these unfit patients are at higher risk for severe toxicity.
For this sub-group of patients, there is no treatment widely accepted as standard and oncologists have to choose among several treatment options: best supportive care, single-agent chemotherapy, non-platinum-based combination chemotherapy and platinum-based combination chemotherapy.
It is still unclear if the benefit achieved with cisplatin-based chemotherapy is restricted only to PS0 and PS1 patients, or also applies to PS2 patients. In the meta-analysis published in 1995, although overall results were limited by statistical heterogeneity and evident outcome differences for the different chemotherapy categories, a significant benefit was demonstrated for cisplatin-based trials, and a sub-group analysis confirmed this benefit for both good and poorer PS patients. However, the outcome of 64 PS2 patients enrolled in the clinical trial ECOG 1594 comparing four platinum-based combinations has proven to be very poor. As for the role of carboplatin, the results of the CALGB 9730 study, comparing paclitaxel plus carboplatin versus paclitaxel alone, must be considered. In the sub-group of PS2 patients median survival in the group treated with combination chemotherapy was significantly longer than with paclitaxel alone. In a randomized phase II study carboplatin plus paclitaxel and cisplatin plus gemcitabine, administered at attenuated doses, proved to be feasible in PS 2 patients. After 1995, some advantage of chemotherapy versus supportive care alone has been shown also with many new cytotoxic agents as gemcitabine, vinorelbine, paclitaxel and docetaxel, administered as single agents. These drugs are usually characterised by a good tolerability, with a low incidence of severe adverse events. Most of the studies show some advantage of chemotherapy in terms of overall survival also in the sub-group of PS2 patients, although formal statistical comparisons are precluded by the low absolute number of patients. However, there is no consistent evidence that combination chemotherapy without platinum is better than third generation drugs given as single agents. An Italian randomised trial compared the combination of gemcitabine and vinorelbine to the two single drugs in patients >70 years of age, and the combination did not show advantage over mono-chemotherapy in terms of overall survival also in the sub-group of PS2 patients. The results of an European Experts Panel on the topic, indicate that single-agent chemotherapy could be the preferred option in the treatment of PS 2 patients, with carboplatin-based or low-dose cisplatin-based doublets representing alternative options. To date randomised trial in USA (carboplatin+ gemcitabine vs gemcitabine) and in Italy (cisplatin+gemcitabine vs gemcitabine) are ongoing. In the near future, the role of targeted agents with better safety profile than chemotherapy as the EGFR-TKI erlotinib, has to be explored in the first-line treatment of advanced NSCLC PS2 patients.

Special Session (Tue, 22 Sep, 17:00−18:00)
Deficient mismatch repair (dMMR) in colorectal cancer

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Defect Mismatch Repair System (dMMR): always genetic and sometimes hereditary

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Lynch syndrome, also called Hereditary NonPolyposis Colorectal Cancer (HNPCC), accounts for about 5% of colorectal cancers and is caused by a germline mutation in one of the mismatch repair (MMR) genes. Colorectal cancer is the most common type of cancer in Lynch syndrome. Also, extra colonic carcinomas occur, i.e. carcinomas of the endometrial, ovaries, small bowel, stomach, sebaceous gland, biliary tract, and upper urinary tract. Typical Lynch syndrome families show an autosomal dominant predisposition of cancers associated with Lynch syndrome, and over 90% of colorectal cancers have a defect in the MMR system (dMMR). Germline mutations have been identified in the MMR genes MLH1, PMS2, MSH2 and MSH6.
Microsatellite instability (MSI) analysis and immunohistochemical (IHC) staining of MMR proteins can detect a defect in the MMR system (dMMR). This defect can be caused either by a germline mutation in the MMR system or by somatic hypermethylation of the promoter region of MLH1. A tumour that shows MSI without staining of MLH1 and PMS2 proteins and with somatic hypermethylation of the MLH1 promoter is characteristic for sporadic cancer, meaning not hereditary.
A disease causing germline mutation can be identified in 60% of patients suspected of Lynch syndrome with an MSI positive tumour (dMMR), 20% show hypermethylation of the MLH1 promoter and therefore do not have a hereditary but a sporadic type of cancer. Interestingly, the remaining 20% of patients, with an unexplained MSI positive tumour, had a less pronounced family history, but were diagnosed at an age comparable to that of proven Lynch syndrome patients.
Differentiation of sporadic CRC from Lynch syndrome-HNPCC is important as surveillance in the latter is more intensive and can reduce mortality from cancer in patients and their close relatives. The finding of a predisposing germline mutation will determine who is (and who is not!) a candidate for participation in surveillance programs. Identification of Lynch syndrome only by family history is insufficient and new strategies are needed to detect more patients at risk for Lynch syndrome.
To improve the identification of Lynch syndrome, we started to implement a new approach called MIPA (MSI indicated by a Pathologist): pathologists select newly diagnosed patients with colorectal cancer for MSI analysis based on one of the following criteria:

1. Colorectal cancer before the age of 50 years;
2. Second colorectal cancer before the age of 70 years;
3. Colorectal cancer and a Lynch associated cancer before the age of 70 years (Endometrial, ovarian, gastric, hepatobiliary, small bowel cancer or transitional cell carcinoma of the renal pelvis or ureter)

Next, the treating physician discusses referral to genetic counselling with patients who have a tumour with MSI indicating deficient MMR.
The newly proposed approach, in which pathologists select patients for MSI analyses, is found to be effective, efficient and feasible in daily practice. Deficient MMR is an excellent marker to distinguish sporadic CRC from patients at high risk for Lynch syndrome, but not all patients with dMMR have hereditary cancer. Therefore deficient MMR is always genetic and sometimes hereditary.

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Should patients with dMMR be treated with chemotherapy?

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The selection of patients to treat with adjuvant chemotherapy for resected colorectal cancer is of outmost importance, in order to decrease the NNT (Number Needed to Treat), chiefly in stage II individuals, who have a relatively good prognosis after surgery alone. In the last few years, patients with colon cancer demonstrating Microsatellite instability (MSI-H) or defective DNA mismatch repair (dMMR) have been reported to have improved survival and to receive decreased or no benefit from 5-FU based adjuvant therapy as compared to patients with microsatellite-stable (MSS) tumors (Ribic C, JCO 2003).