1215 PUBLICATION

Is routine chest X-ray (CXR) a useful part of follow up in all adult patients with soft tissue sarcoma?

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Background: Soft tissue sarcomas in adults are relatively rare. After treatment of localised disease the common site of relapse is either locally or in the lungs. Routine surveillance of the lungs is justified because surgical intervention may be curative. In Edinburgh patients are routinely followed up on a six monthly basis with CXR to screen for lung metastases. The radiation exposure over a standard 10 year follow up is not insignificant, and it is unclear if all patients, irrespective of the initial grade of their primary tumour, require this.
Aims: To determine the pick up rate of lung metastases by routine CXR over a 10 year period in patients diagnosed with soft tissue sarcoma, and to review the primary histology.
Methods: Adult patients diagnosed with a localised primary soft tissue sarcoma and all those on routine follow up between 1994 – 2004 were identified on the departmental data base and the notes of those with lung metastases reviewed. Data was collected on their initial histology, and date and method of diagnosis of lung metastases.
Results: 179 patients were under follow up during this 10 year period. 24 (13.4%) developed lung metastases, and 22 sets of notes were found. 6 (27%) had metastases diagnosed by routine CXR, 9 (41%) had metastases diagnosed by non routine CXR and 7 (32%) had metastases diagnosed by CT as staging for local recurrence or as investigation for a general decline in health. On review of histology none were grade 1, 4 (18%) were grade 2 and 18 (82%) were grade 3. 155 patients therefore received 6 monthly CXR for 10 years without developing lung metastases, and hence possibly unnecessarily. Total patient years at risk were 512.24, equating to 1 patient developing lung metastases for every 21 years of follow up.
Conclusion: Lung metastases occur in a minority of patients (13.4%) and most (82%) occurred in patients with grade 3 tumours. No patients with grade 1 tumours developed lung metastases. 73% of lung metastases were diagnosed by investigations prompted by symptoms or as part of staging for recurrence elsewhere. Thus routine CXR may be appropriate on grade 3 tumours, but not on lower grade tumours.

1216 PUBLICATION

Intron A: Health Management Program (HMP) in high-risk malignant melanoma showed the positive impact of hydration

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Background: Skin cancer affects more then 75,000 Canadians each year. Malignant melanoma is rare but accounts for >75% of all skin cancer deaths and the incidence is increasing at an annual rate of 2%. Intron A is the only adjuvant therapy that has increased survival in high-risk melanoma patients. However side effects may lead to early discontinuation of therapy or sub-optimal drug exposure.
Methods: Patients were educated on the benefit of therapy and were given comprehensive patient education materials. Oncology nurses provided support to help patients better manage and control adverse events.
Results: A total of 251 patients were scheduled to receive 20 MIU/m^2 5 days a week for 4 weeks followed by 10 MIU/m^2 3 times a week for 48 weeks. Twenty-nine percent of patients progressed before completion of therapy. Of the remaining patients, 52% completed a full year of therapy, with 93% of those patients being compliant more than 80% of the time. The majority of discontinuations occurred during the induction phase (57%) vs during the maintenance phase (43%). Males were more likely to be compliant than females ($p < 0.05$), especially during the first few months of the maintenance phase. The two most common reasons for discontinuation were adverse events (58%), and disease progression (29%). Patients with fluid intake >1.5 liter/day were more likely to complete therapy (64%) compared to those drinking a smaller volume (32%, $p < 0.0001$). The impact of hydration could be seen both during the induction and maintenance phase.
Conclusion: A significant proportion of melanoma patients who receive high dose Intron A therapy discontinue early due to adverse events. The importance of fluid intake was clearly established by the Intron Health Management Program, since it was the most favorable predictor for completion of therapy.

1217 PUBLICATION

Treatment for isolated local recurrence of soft tissue sarcoma arising in a previously irradiated field

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Purpose: To evaluate outcome and treatment toxicity in patients undergoing wide local excision (WLE) with or without brachytherapy (BRT) for soft tissue sarcoma (STS) recurrence arising within a previously irradiated field.
Methods: A retrospective review was performed of 59 patients who were treated for isolated local recurrence of STS. All patients underwent prior resection and external beam radiation (median dose 51 Gy, range 40–69 Gy). For recurrent disease, 22 patients were treated with WLE alone and 37 with WLE and an after-loaded BRT single plane implant. Iridium 192 wires were loaded 3 to 12 days postoperatively. The prescribed BRT dose was 45 or 50 Gy. Anatomic locations included extremities (N = 37), trunk (N = 16), and head and neck (N = 6). The most common histology was malignant fibrous histiocytoma (MFH) (N = 33).
Results: With a median follow-up time of 45 months, the 4-year disease specific survival rate was 80%. The 4-year actuarial local control (LC) rate and distant metastasis free survival (DMFS) rate were 48% and 75%, respectively. Multivariate analysis revealed that positive surgical resection margins ($p = .013$) and non-extremity tumors ($p = .005$) were associated with lower rates of LC. No factors predicted for rate of DMFS. The actuarial late complication rate was 52% at 4 years, and of 32 patients with late complications, 15 required surgical intervention (2 amputations). Among 37 patients with extremity tumors, 23 maintained normal daily function, 9 had limited disability, 4 had disabilities requiring medical treatment, and 1 had disability requiring surgery. The 4-year amputation free survival rate for these patients was 74%. Although patients treated with BRT were more likely to have MFH ($p = .02$) and high grade tumors ($p = .03$), there were no significant differences in outcome or complication rates between patients receiving and not receiving BRT.
Conclusion: WLE, with or without BRT, for recurrent, previously irradiated STS may prevent or delay amputation in most patients with extremity recurrences. In this series, however, treatment was associated with significant late wound complications and a less than satisfactory rate of LC. Despite 68% of patients having high-grade tumors, only 25% developed distant disease at 4 years, suggesting that the predominant pattern of failure is local. Limb and function-sparing treatment is therefore worthwhile, but techniques for avoiding serious wound complications and improving LC must be pursued.

1218 PUBLICATION

Classical Kaposi's Sarcoma: efficacy of single high dose radiotherapy

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Purpose: To evaluate the efficacy of single fraction of high dose radiotherapy in patients with classical Kaposi's sarcoma (CKS).
Methods and materials: Between June 1994 and February 2005, 46 patients with cutaneous CKS were treated based on a prospective study in Hacettepe University, Department of Radiation Oncology. Thirteen (28%) patients had received chemotherapy before radiotherapy and referred due to recurrent or progressive disease. Twenty-four (52%) patients who had disseminated disease were given chemotherapy following radiotherapy. All the lesions were treated locally with 2–3 cm safety margin with 4–6 MeV electron beams. The radiotherapy was in the form of single fraction of 8 Gy in the first 4 years. After finding out the high efficacy of 8 Gy in 1998, the dose was reduced to 6 Gy in order to find the lowest effective dose.
Results: Median follow-up time is 48 months (1–128 months). The male-to-female ratio was 3.6:1. The median age of onset among CKS patients was 61 years (range, 18–87). Of 46 patients, 8 (17%) had an underlying immunocompromised state and 1 (2%) had a previous diagnosis of Hodgkin's disease. The majority of patients responded to radiation therapy. Of 207 fields treated, 51 and 152 fields were treated with 8 Gy and 6 Gy, respectively. The overall objective response rates (complete and partial) were 69%, 88%, 84% and 89% at 1, 3, 6 and 12 months, respectively.

Complete response rates at 1, 3, 6, 12 months were 43%, 73%, 76% and 93% for 8 Gy and 32%, 62%, 60% and 55% for 6 Gy. There was significant difference between complete response rates of 8 Gy or 6 Gy at 12 months ($p < 0.001$). Side effects were tolerable in all but 3 patients who experienced fibrosis and edema.
Conclusion: Radiotherapy is an effective mode of treatment for localized Kaposi's sarcoma and it seems that single dose of 8 Gy is more effective than 6 Gy for long-term local control.

1219 PUBLICATION

Methionine-free diet in association with nitrosoureas treatment of metastatic melanomas: Methionine-free diet duration and modulation of O6-methylguanine-DNA-methyltransferase

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Background: In *in vitro* and *in vivo* experiments, Methionine (MET) depletion used in association with cytostatic drugs has been shown to improve of their therapeutic index. One hypothesis by which MET deprivation sensitized these tumors to nitrosoureas (CENUs), could be attributed to down-regulation of the repair protein O6-methylguanine DNA methyltransferase (MGMT), one of the main mechanisms of resistance to CENUs. On the basis, we initiated a phase I clinical trial associating dietary MET restriction with nitrosourea treatment (cystemustine) for metastatic melanomas. We determined the optimal MET-free diet duration and evaluated the feasibility of this association and its impact on MGMT activity in peripheral blood mononuclear cells (PBMCs) during treatment.
Material and methods: Ten patients received 2 months of treatment, i.e. 4 cycles every two weeks of the association of MET-free diet and nitrosourea treatment (Cystemustine 60 mg/m^2). During each cycle, patients received standard diet the 1rst day and then MET-free diet, which allowed testing randomly 4 periods of 1, 2, 3 or 4 regime days. Daily concentrations of plasma MET, before and after diet nutritional status (BMI and PINI determinations) and toxicity were evaluated. Every cycle, MGMT activity level was measured by HPLC in PBMCs isolated on ficoll from blood samplings before and after diet period.
Results: Dietary MET restriction reduced MET concentrations from 21.21.3 μM before diet to 12.01.0 μM from only one day of diet, with a mean optimal decline of 41%. No cumulative effect have been observed despite the lengthening of MET-free diet duration. MET-free diet have not deleterious effect on nutritional status. The toxicity OMS grade 3–4 remained moderated (3/10 thrombopenia and 3/10 neutropenia). Comparing before and after diet period (analysis of 6 patients), the MGMTactivity in PBMC of these patients was not affected by MET restriction (434±108 fmol/mg before MET-free diet vs 354±49 fmol/mg after MET-free diet). Individual interpatient variability of MGMT activity was very important, ranged from 83 to 1424 fmol per mg of protein. However, plasma MET variation (before and after diet) seemed to be correlated with the MGMT activity variation.
Conclusions: A 1 day MET-free diet will be adopted to realise a phase II clinical trial aimed at evaluating the therapeutic efficacy and toxicity of the association of MET restriction diet with nitrosourea treatment. Concerning modulation of MGMT activity, these preliminary results might be confirmed and would be explored on phase II clinical trial patients.

1220 PUBLICATION

Intraoperative electron beam therapy (IOERT) combined with EBRT in the treatment of retroperitoneal sarcomas

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Purpose: Complete surgical resection remains the mainstay of treatment of soft tissue sarcomas (STS) located in the retroperitoneal space, but is possible only in 60–70% even in patients presenting with primary disease. Randomized trials have demonstrated improved local tumor control for patients with extremity STS after postoperative radiotherapy (EBRT) whenever doses of 60–70 Gy can be administered. As EBRT in retroperitoneal STS is limited by tolerance doses of surrounding tissues, additional IOERT was used to overcome these dose limitations.
Methods: From 1991 to 2003, 67 patients (m/f 38:29) with retroperitoneal STS (primary disease 31, recurrent disease 36) were treated with maximal resection, IOERT and EBRT. Median age was 54 years. Tumor grading was G1 in 5 (7%), G2 in 20 (30%) and G3 in 42 patients (63%). Mean tumor size was 10.5 cm. Most common histology was liposarcoma (50%). Mean IOERT dose was 15 Gy. Electron energies ranged from 8 to 15 MeV. IOERT was delivered to the complete tumor bed if possible. Postoperative EBRT was given to 94% of our patients with doses of 39.6–50.4 Gy (mean 42.5 Gy) in 1.8 Gy per fraction. EBRT was delivered by linear accelerator with photon energies ranging from 6 to 23 MV after CT-based 3D treatment planning.
Results: Median follow up was 20 months. Complete resection was possible in 21 (31%) patients, while 34 patients (51%) showed microscopically, and 12 (18%) patients macroscopically residual disease. 5 year actuarial overall survival was 52%. Primary vs. recurrent status had no significant impact on survival. Actuarial 5 year survival was marginally significantly affected by tumor grade (80% for G1/2 vs. 41% for G3 tumors, $p = 0.06$). After complete resection, 5 year actuarial survival was 70% compared to 45% after R1- and 34% after R2-resection. Actuarial 5 year metastatic-free survival was 54%. The 5 year actuarial local control rates in- and outside the IOERT field were 78% and 54%. Except for 5 patients with postoperative wound healing disturbances, no IOERT related acute complications were seen. Only 2 patients required surgical interventions due to late complications.
Conclusion: Combination of maximal surgical resection, IOERT and EBRT in patients with retroperitoneal sarcomas results in good overall survival, especially in R0 resected patients, without increased toxicity to normal tissue.

1221 PUBLICATION

Genetic characterisation of leiomyosarcoma

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Leiomyosarcoma (LMS) is a malignant tumour of mesenchymal origin displaying phenotypic features of smooth muscle differentiation and accounting for approximately 5–10% of soft tissue sarcomas. Soft tissue sarcomas (STS) are relatively rare compared to epithelial cancer comprising less than 1% of all human cancers.
LMS falls into a group of STS which frequently show complex karyotypic changes and extensive heterogeneity characteristic of severe disturbances in genomic stability. With an overall low long term survival rate, a lack of a tumour specific genetic alteration, and a wide spectrum of histopathological features and clinical behaviour, progress in the diagnosis, classification and management of these tumours has been limited.
Comparative genomic hybridisation (CGH) was used to characterise a series of paraffin embedded cases of LMS to identify candidate regions containing tumour relevant genes involved in the development of LMS. CGH provides information on regions of amplification and deletion of genetic material across the whole tumour genome in a single hybridisation experiment.
The results have shown chromosomal gains to be more frequent than losses. Among the most common gains and losses, a high frequency of gains were present on 1q, 4q and 6q, and a high frequency of losses involved regions on chromosomes 1p, 8p and 19q. New regions of chromosomal gain and loss occurring in high frequency have also been highlighted. The results suggest these regions of gain and loss may contain oncogenes and tumour suppressor genes, respectively, involved in the development and progression of LMS, and are subject to further investigation.

1222 PUBLICATION

Development of a rapid screening approach for candidate gene sets in cancer

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Background: During the last decade, microarray-based gene expression analysis gave rise to a large number of candidate genes for the diagnostics and therapy of cancer. Bioinformatic approaches delivered gene sets, the expression patterns of which were predictive for certain cancer phenotypes. A synergy between these advances and the development of screening tools for a rapid and reliable screening of marker gene expression represents an important step towards an improved treatment of cancer.
Methods: For the semi-quantitative expression screening of eleven candidate genes for drug resistance in melanoma, we combined multiplex RT-PCR (mRT-PCR) with subsequent microfluidic fragment analysis.
Results: The functionality of this approach was demonstrated by low inter-experimental variations of amplicon quantities after endpoint analysis. Applied to RNA samples derived from drug-sensitive and -resistant melanoma cell lines, mRT-PCR delivered results qualitatively concordant