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Comparative assessment of late toxicity in patients of carcinoma cervix treated by radiotherapy versus chemo-radiotherapy – Minimum 5 years follow up

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ABSTRACT

Background: A randomised trial was carried out comparing chemo-radiation (CTRT) vs. radiotherapy (RT) in patients of carcinoma cervix and showed similar rates of pelvic disease control, disease free survival and overall survival. Late toxicity is presented.

Methods: Between December 2000 and July 2006, 180 patients of carcinoma cervix were randomly assigned to RT + weekly cisplatin (n = 94) or RT alone (n = 86). Late toxicity was prospectively scored using RTOG criteria in 156 evaluable patients, 79 and 77 respectively and is presented as crude incidence for rectum, bladder, small intestine, vagina, skin and bone and also as actuarial incidence for rectum and bladder.

Results: The median follow up of surviving patients was 10.4 years (minimum – 6.5 years). Crude incidence, CTRT vs. RT, of late toxicities were: rectal (7.5% vs. 5%, p = 0.22), bladder (15% vs. 10.4%, p = 0.76), small bowel (3% vs. 1.2%, p = 0.51), vagina (25% vs. 35%, p = 0.35) while the actuarial risk of grades 3–5 rectal and bladder toxicities by 5 years were 13% vs. 10% (p = 0.698) and 16% vs. 14.8% (p = 0.783) respectively. Bladder toxicity appeared later then rectal toxicity (median 49.4 vs. 21.4 months). Severe bone toxicity (fractures) were higher in the CTRT arm, 5% vs. 0%, p = 0.018. On multivariate analysis vaginal involvement (p = 0.016) and bulky tumor (p = 0.020) were associated with severe vaginal morbidity while rectal point dose > 80% (p = 0.040) was associated with a higher incidence of rectal toxicity.

Conclusion: Bone toxicity was significantly increased by addition of CT to RT and patients continued to experience toxicity at longer periods of follow up albeit disease free.

Background

The National Cancer Institute (NCI) issued a clinical alert in 1999 [1] for the use of chemoradiotherapy (CTRT) in patients of carcinoma cervix based on the results of five randomized trials [2–6]. These trials showed that CTRT decreased the proportional risk of death by 30–50% with an absolute survival benefit of 10–15% when compared to radiotherapy (RT) alone [7,8]. Therefore CTRT has been adopted as the standard of care across the world, for high-risk early stage and locally advanced cancers of the cervix although the latter cohort was poorly represented in these trials. A more recent meta-analysis of trials confined to locally advanced cancer cervix excluding trials with any surgical interventions confirms the improved loco-regional control rates and survival advantage of CTRT, albeit at the expense of enhanced acute morbidity [9]. A systematic review and meta-analysis of individual patient data from over 4800 women and 18 randomized trials endorsed the recommendations made by the NCI, but showed that the benefits of chemoradiotherapy on survival were smaller than previously thought (absolute benefit 6%) with a further reduction in magnitude of effect with advancing stage (3% absolute benefit in stage III, IV) [10]. An increase in haematological and acute gastrointestinal toxicity was confirmed. Late toxicity reporting was available only in few of the included trials while insufficient or no data were available for most. A review of literature reveals that late toxicity data is sparse due to short follow up and inadequate data recording and reporting [11,12].

The present phase III trial evaluated the role of CTRT vs. RT in patients with stages IIB-IVA of cervical cancer and reported similar rates of pelvic control, disease free survival (DFS) and overall survival (OS) and was included in the meta-analysis referred to (9, 10). Late toxicity assessment was a secondary outcome measure in this study. The present report therefore focuses on late morbidity.

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Patients and methods

Following an informed written consent and approval of the Institutes ethics committee, patients with a previously untreated histology proven squamous or adenocarcinoma of the intact uterine cervix were recruited in a phase III trial. They underwent a history and physical evaluation, routine hematological and biochemical blood tests, a chest X-ray and a contrast enhanced CT scan of the thorax, abdomen and pelvis and staged based on the FIGO 1997 staging system [13].

Inclusion criteria were age < 75 yrs; Karnofsky performance scale (KPS) ≥ 60; stages IB-IVA (visceral and bone metastasis excluded); adequate hemoglobin (Hb) > 10gm% (following blood transfusions as required) and adequate renal function. Patients were randomized into two arms using a table of random digits without stratification for any prognostic variables. In the CTRT arm, they received chemotherapy (CT) consisting of once-a-week cisplatin (CDDP) 35 mg/m^2 (capped at 50 mg) concurrently with external beam RT (EBRT), 50 Gy in 25 fractions over 5 weeks at 2 Gy per fraction (delivered using a telecobalt machine or a linear accelerator with 2 or 4 field technique) followed by intracavitary radiotherapy (ICRT) (delivered using either a Microselectron-HDR (Nucletron, The Netherlands) or Ralstron 20B (Shimadzu, Japan) after loading machine). Patients were treated with 6 Gy per fraction, high dose rate (HDR) prescribed to point 'A' for 3 insertions, spaced a week apart and planned using orthogonal X-rays for each insertion. Dose prescription and bladder and rectal point dose recording were based on ICRU 38 guidelines [14]. Patients randomised to RT were treated with an identical RT protocol without CT. Acute morbidity was recorded during and up to 3 months of completion of therapy using the RTOG criteria.

Following completion of treatment, patients were assessed at monthly intervals for the initial 3 months and 3 to 6 monthly intervals thereafter. Persistent/recurrent disease was confirmed with a biopsy and late toxicity was graded according to the RTOG/EORTC scoring criteria [15]. Morbidity from grades 0 to grade 5 were recorded and those with severe morbidity (grade 3–5) were grouped together and analysed for comparison between two arms except for vaginal toxicity where it was scored as mild –i.e. adhesions without stenosis, or severe – i.e. stenosis and shortening of vagina. Late complications were considered to be those occurring 90 days or beyond from the day of start of radiotherapy. Patients lost to follow up (prior to 90 days following completion of all therapy) were excluded from toxicity analysis as it would then likely underestimate the real incidence of late toxicity. Patients not reporting during follow up were contacted telephonically. In case that was not possible then questionnaires were mailed to them.

Statistical analysis

All time intervals were measured from the date of start of RT. Date of appearance, peak and resolution of bladder and rectal toxicity were recorded and helped to compute actuarial estimates of late toxicity for these two sites, while crude incidences were documented for all sites. When computing actuarial complication rates, patients who died without experiencing a complication were censored at the time of death, and surviving patients or those lost to follow - up were censored at the date of last contact. The Kaplan-Meier method was used to compute actuarial estimates and statistical significance of difference between groups ascertained using the Log-rank test. Statistical significance of difference in proportions or differences in means was computed using the chi square test or 't' test respectively. Logistic regression method was used to conduct multivariate analysis of different demographic, tumour and treatment related factors.

Results

Between December 2000 and July 2006, 180 patients were included and randomised to CTRT, n = 94 or RT, n = 86. Median follow-up of the surviving patients was 10.4 years (range 6.5–13.2). The demographic characteristics were matched in the 2 arms; median age 50 years; most patients fit (median KPS 80); bulky disease i.e. > 4 cm predominated (55%); squamous cell carcinoma was the predominant histology (97%) with advanced presentations i.e. Stage IIB (47%) and IIIB (43%) being common (Table A1).

Interventions (Table A2)

The majority of patients received EBRT to the whole pelvis by 4 field box technique, 89% (160/180) while the remaining received an AP/PA field, while 3 ICRT applications were completed in 87% (156/180). For reasons of machine breakdown, 2 patients were referred to another centre and treated with a low dose rate ICRT.

Chemotherapy

Ninety two of the 94 randomised to CTRT arm, received the planned course of treatment; one patient did not report for treatment after 1 week and 1 did not receive chemotherapy due to an administrative error. Similarly, 2 patients in the RT alone arm received CT: due to an administrative error. Seventy nine percent patients received 5cycles or more, 12% 4 cycles and 2% 3 cycles of chemotherapy.

Survival

The overall survival(OS) local progression free survival (LPFS) and distant disease free survival(DDFS) at 5 yrs for CTRT and RT arms were 39.4% vs. 37.2% (p = 0.709) 52% vs. 49.4% (p = 0.993) and 44.6% vs. 41.4% (p = 0.802) respectively. The overall LPFS for tumors > 4 cm vs. < 4 cm was 48% vs. 39.5% (p = 0.063, median 59.7 months vs. 38.7 months) for the entire cohort.

Acute toxicity

Anemia, leucopenia, upper GI and skin toxicity (nausea) was significantly higher in CTRT arm. The differences were significant for mild toxicity but were not for severe toxicity (> = grade 3) between both the arms. There were no acute toxicity related deaths (Table A3).

Late morbidity

Out of 180 patients, late toxicity assessment was possible in 156 cases. 21 patients were not evaluable for reasons of lost to follow up and records of 3 patients could not be accessed. Out of the total evaluable patients, 79 were in CTRT arm and 77 in RT arm.

The crude incidence of late complications was broadly similar in both the arms with (32/156) 20.5% of patients experiencing at least one complication that was classified as severe toxicity.

Bone toxicity leading to fracture was significantly higher in the CTRT s compared to RT alone (5% vs. 0%, p = 0.018). One patient had resorption of the head of femur, second patient had pubic/acetabular fracture, one patient each underwent Total Hip replacement and femoral prosthetic implant respectively but the site of fracture was not documented. The crude incidences of toxicity of other scored organs were not significantly different (Table 1).

Actuarial Estimates and time trends for Bladder and Rectal Toxicity (Figs. 1 and 2).

The actuarial 5 year estimates of rectal toxicity (all grades) were 48% and bladder toxicity of 37% for the entire group. The actuarial risk for development of major rectal complication (Grades 3–5) at 5 years was 13% and 10% for and B respectively (p = 0.698). The actuarial risk for development of major bladder complication at 5 years was 16% and 14.8% for and B respectively (p = 0.78). Median time for the development of rectal bleeding was 21.4 months, (range 6–24.5 months). Median time for the development of bladder bleed was 49.4 months (range 6–147