The prognostic significance of β human chorionic gonadotrophin and its metabolites in women with cervical carcinoma

Robin A F Crawford, Ray K Iles, P G Carter, Carole J Caldwell, John H Shepherd, Tim Chard

Abstract

Aims—To examine long term survival of women with primary and recurrent cervical carcinoma in relation to (1) excretion of β-core (a urinary metabolite of β human chorionic gonadotrophin (βhCG)) and (2) βhCG immunostaining of the tumours, to determine the suitability of these markers for assessing prognosis.

Methods—This was a prospective observational study undertaken in a gynaecological oncology centre: 57 women with primary cervical cancer and 42 with recurrent disease were recruited between January 1990 and September 1992. Kaplan–Meier survival analysis with the log rank test was used to assess survival differences with survival rate given per year of follow up.

Results—In primary disease, the four year survival for the β-core negative group was 79%, compared with 14% for the β-core positive group (p = 0.001). This was still significant for early stage disease or squamous lesions alone. In recurrent disease, β-core positivity was not prognostically significant. Immunohistochemistry was of no prognostic significance in either group.

Conclusions—β-core excretion appears to be useful in assessing prognosis of primary cervical cancer but not of recurrent disease. A large prospective study of urinary β-core in early stage cervical cancer is needed to determine whether it can be used as an index for modifying treatment.

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However, the clinical use of free βhCG as a tumour marker has been limited to a small number of patients owing to a short half life and rapid renal clearance. Attention has therefore been focused on urine metabolites, in particular β-core, which is produced as a result of the intrarenal metabolism of βhCG. The majority of hCG immunoreactivity in urine is accounted for by β-core. Excess β-core is associated with gynaecological cancer (reviewed by Cole et al"). In a previous study from our group, we reported that β-core was a significant prognostic indicator for premenopausal women with primary cervical cancer followed up for only 18 months.

We now report the long term outcome of a group of patients with primary and recurrent cervical cancer in relation to urinary excretion of β-core. Some of these patients were included in our previous report. In addition, we report the results of immunohistochemical staining of the tumours for βhCG.

Methods

The study included consecutive patients presenting with cervical cancer (primary and recurrent) at St Bartholomew's Hospital and the Royal Marsden Hospital between January 1990 and September 1992. Local research ethics committees had approved the protocol. Fifty seven women with primary disease and 42 with recurrent disease were identified. All patients with recurrence had already received pelvic radiotherapy. A representative block was selected for each patient from archival tissue and 3 µm sections were mounted on coated slides for immunohistochemistry. An adjacent slide was stained with haematoxylin and eosin for reference. The histological diagnosis was reviewed by CJC.

Human chorionic gonadotrophin (hCG) is a valuable tumour marker for trophoblastic disease and germ cell tumours. In addition, synthesis of free βhCG and its subunits by pelvic carcinomas such as those of the colon, urinary tract, prostate, uterus, and vulvo-vagina has been reported. The presence of increased serum levels of hCG and its metabolites is generally agreed to be a sign of a poor prognosis and it has been suggested that hCG might directly modify the growth of the cancer, leading to a worse outcome. Furthermore, positive immunohistochemical staining for βhCG is also associated with a survival disadvantage following radiotherapy.

βhCG Samples suitable for immunohistochemistry were available from 46 patients with primary cervical cancer and from 29 with recurrent disease. For immunohistochemistry, sections were dewaxed and then pressure cooked for four minutes at 103 kPa as the method of antigen enhancement. A rabbit polyclonal anti-βhCG antibody (Dako, High Wycombe, UK) was used at a dilution of 1:5000 overnight at 4°C. A standard indirect avidin–biotin immunoperoxidase technique was then applied. A section of placenta was used a positive control, and the primary antibody was substituted with non-specific rabbit antibody as negative control.
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The median age of this group was 45 years (range 23 to 82 years) and 35 women were premenopausal. There was no age related survival advantage in this group of women comparing young women (<40 years) with older women, nor any relation to menopausal status. There were 28 cases with stage 1 disease, 11 with stage 2, 10 with stage 3, five with stage 4, and no record in three cases. Forty cases were squamous cell carcinoma, eight were adenocarcinoma, and seven had adenosquamous lesions (identified with periodic acid Schiff and alcian blue (PAS/AB) staining in addition to H&E). In two cases the pathology was not recorded. The median time to death or date of census (April 1996) was 35 months (range 1 to 74 months). Follow up information was not available in two cases.

Recurrent cervical cancer

The median age of this group was 45 years (range 25 to 78 years). The median survival from initial diagnosis of cancer was 22 months (range 2 to 149 months). At initial diagnosis, there were 19 cases with stage 1 disease, 13 with stage 2, five with stage 3, four with stage 4, and no record of initial stage in one case. Thirty cases were squamous cell carcinoma, five were adenocarcinoma, and five had adenosquamous lesions. The original histology was not recorded in one case. The median survival time from diagnosis of recurrent cancer, when the urine marker was investigated, was eight months (range 1 to 71 months). The five year survival of this group from presentation with recurrent cervical cancer was 10%.

**PATIENT CHARACTERISTICS**

**Primary cervical cancer**

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**RESULTS**

**PRIMARY DISEASE**

Thirty one patients were β-core negative and 15 were β-core positive. The four year survival for women who were β-core negative was 79%; the four year survival of the β-core positive women was only 14% (log rank test: \( \chi^2_{(2)} = 19.74; p = 0.001 \)) (fig 1). This survival difference was also seen when early (stage 1) and late stage (stage 2 and more advanced) disease was compared (five year survival for β-core negative and early stage, 95%; median survival for β-core negative and late stage, 37%; no survivors at one year for β-core positive and early stage, median survival eight months; median survival for β-core positive and late stage, 12%; log rank test: \( \chi^2_{(2)} = 28.52; p = 0.001 \)) (fig 2). Women with squamous lesions also showed a significant survival advantage in the β-core negative group (two and four year survival for β-core negative women 79%, β-core positive women 10%, \( \chi^2_{(2)} = 19.74; p = 0.001 \)) (fig 1).

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**FIGURE 1** Kaplan-Meier survival curve for patients presenting with primary cervical cancer separated on the basis of the urinary β-core measured at presentation (log rank test: \( \chi^2_{(2)} = 19.74; p = 0.001 \)). β-Core negative group: \( n = 30; \) six events; five year survival 79%. β-Core positive group: \( n = 14; \) 11 events; median survival 12 months, four year survival 14%.

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**FIGURE 2** Kaplan-Meier survival curves for patients presenting with primary cervical cancer separated on the basis of β-core and stage (log rank test: \( \chi^2_{(2)} = 28.52; p = 0.001 \)). β-Core negative/early stage: \( n = 20; \) one event; five year survival 95%; β-core negative/late stage: \( n = 10; \) five events; median survival 37 months. β-Core positive/early stage: \( n = 3; \) three events; median survival eight months; β-core positive/late stage: \( n = 11; \) eight events; median survival 12 months.
The urine samples of 11 of the 57 patients with primary cancer and four of the 42 patients with recurrent cancer were too dilute for β-core analysis. This may have introduced bias, but as the samples were analysed in batches it was not possible to collect further specimens from these patients.

A tissue specimen is always taken at the time of diagnosis of primary and recurrent disease. The presence of βhCG can be detected using immunohistochemistry and might obviate the need for a urine test (β-core). However, in the present study βhCG staining was of no prognostic value in any group. This might be related to technical problems, although we used an appropriate antigen retrieval method. The more likely explanation is that βhCG is released rapidly following synthesis with little or no storage in the cell, and a random section of the tumour will be unlikely to contain more than a few positive cells at most. The small amount of staining in cases which were counted as positive is in contrast to positive transitional cell bladder carcinomas which show widespread staining. This suggests that the positive areas might represent non-specific staining. In colorectal cancer, the prognostic significance of raised serum βhCG as a tumour marker was significant for poor outcome while immunohistochemical staining was of no value. These findings are reflected in our study.

The expression of βhCG is stage related. Two of the three women who were β-core positive in the early stage subset of the primary group had involved pelvic lymph nodes. Therefore, larger numbers are required to determine whether the β-core expression and poor outcome are related to a larger tumour volume rather than to more aggressive disease. With the increased effectiveness of the United Kingdom national cervical screening programme, there has been a considerable fall in mortality and a reduction in the frequency of advanced disease. In advanced stage disease, the treatment options are limited to radiotherapy with or without adjuvant chemotherapy. Only in early stage disease, however, is there a significant potential for treatment modification, with tailoring the extent of surgery to suit the individual case with its prognostic indicators. In the woman with an early stage cancer and negative β-core, consideration may be given to a fertility sparing type procedure if indicated. In those women with positive β-core, the use of chemo-radiotherapy rather than surgery may be more appropriate. A large prospective study of urinary β-core in early stage cervical cancer is needed to ascertain whether it can be used as an index for modifying treatment.

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