A Positive Beta HCG:
Time for a resurrection in the role of beta HCG in muscle invasive bladder cancer? – A mini-review

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Muscle invasive bladder cancer has a poor prognosis; even if diagnosed early and treated promptly there is an overall survival for all stages of around only 50%. This highlights the need for more targeted therapies in bladder cancer management, analogous to those that exist in the management of other solid tumours such as breast cancer. Currently there are targets such as FGFR3, EGFR and P53, which have produced promising results. However, at present there are no recommended biomarkers for use in the everyday clinical management of patients with bladder cancer. This mini-review will look at beta-HCG (βhCG) as a potential marker, which the authors feel deserves a resurrection in its interest and use as a potential target in the management of muscle invasive bladder cancer.

Bladder cancer is the 9th commonest cancer diagnosis worldwide with more than 330,000 new cases diagnosed, and more than 130,000 lives claimed by it each year [1]. Over 90% of bladder cancers arise from the urothelium and are described as transitional cell carcinomas. The remaining variants are made up of squamous cell carcinomas, adenocarcinomas and the rarer subtypes including lymphoma, melanoma, leiomyosarcoma and small cell carcinoma [2].

The usual mode of presentation is painless haematuria. Approximately 70% of new cases are classified as superficial disease, which means that the tumour has not invaded deeper than the lamina propria. This type of bladder cancer is primarily managed endoscopically, plus or minus the addition of disease modifying intravesical agents such as Mitomicin C and BCG. The prognosis of superficial bladder cancer is very good, with survival rates of over 90%. The remaining patients will progress from superficial disease to muscle invasive disease. Approximately 30% of patients present de novo with muscle invasive disease [3]. This is when the tumour has invaded through the lamina propria into the underlying muscle and eventually beyond. In this scenario the disease behaves very differently, with an overall 5-year survival of approximately 50% [4].

The gold standard treatment for muscle invasive bladder cancer remains radical cystectomy. However, radical radiotherapy can be used as an alternative, although cancer specific outcomes are arguably not so favourable. The role of neo-adjuvant chemotherapy is now well established. Although no individual trial has shown a survival benefit with its administration, the meta-analysis of the trials shows an overall, absolute survival benefit of 5% with neo-adjuvant chemotherapy [5].

Post-cystectomy, follow-up for disease recurrence varies between centres. The regime used is based on the pathological stage of the initial tumour at cystectomy and involves regular USS of the renal tract, CT/MRI of the thorax and abdomen, serum biochemistry and urine cytology. However, the exact interval between imaging is not currently agreed. The dilemma with active surveillance of these patients is whether there are any effective treatments that would be beneficial if a diagnosis of an early recurrence was made. Some authors have found no benefit of actively monitoring these patients over simply treating symptoms as they arise [6]. However, with increasing developments in research it may soon be possible to personalise chemotherapy in this setting.

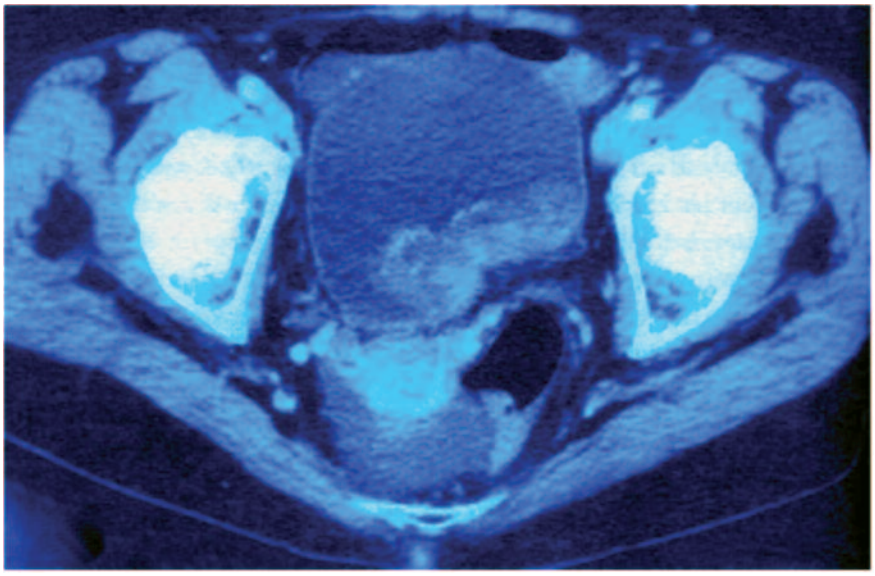
Compared to other solid tumours, there is a real lack of prognostic markers that have been identified for targeted therapies in this disease. We feel that βhCG is a more or less forgotten target that deserves further research.

What is human chorionic gonadotrophin (HCG)?

HCG is a heterodimeric glycoprotein comprising two non-covalently bound subunits named 'alpha' and 'beta'. The alpha subunit comprises a 92 amino acid sequence [7] encoded by a single gene located on chromosome 6q21.1-q23, and is common to all members of the glycoprotein family including thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH) and luteinising hormone (LH). The beta subunit however, is unique to HCG and comprises a 145 amino acid sequence. It can be encoded for by any one of six non-allelic genes; β1,2,3,5,7 and 8, present on chromosome 19q13.32 [7].

HCG is perhaps best known for its physiological role in pregnancy where it is initially secreted by the developing embryo and later by syncytiotrophoblasts of the placenta. In pregnancy it has a number of described roles such as promoting angiogenesis of the uterine vasculature, stimulating foetal testosterone production and enhancing corticosteroid production and maternal immunosuppression to prevent rejection of the foetus and placenta [8].

Physiological production of low levels of HCG by the pituitary in healthy males and females of all ages has also been described, with slightly higher levels of pituitary HCG being produced by peri- and post-menopausal women [9].



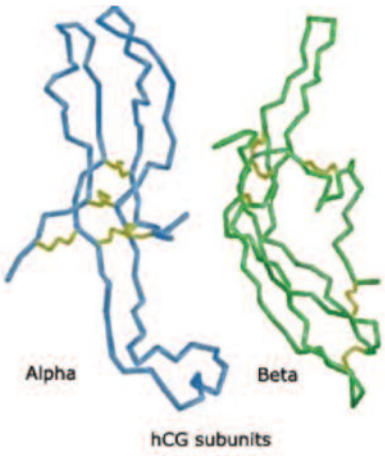


Table 1: A summary of the results of previous research studying ßhCG expression in bladder cancer

T-stage	% with positive serum βhCG	% over-expressing βhCG immunohistochemically
T0	10%[33]	30%[34]
T1	23-30%[29,34,35]	20-42%[32,34,36]
T2-4	27-65%[29,31,33,34]	25-63%[31,32,34,36]
Metastatic	20-76%[33,37]	100%[32]

Growth effects in bladder cancer

In vitro studies of bladder, cervical and endometrial cancer cell lines have demonstrated an increased rate of replication with the addition of βhCG to the culture medium [10]. These growth effects may be attributable to its crystal structure, which has proven to be structurally akin to the family of cystine knot factors, including nerve growth factor (NGF), platelet-derived growth factor (PDGF-B) and transforming growth factor (TGF-β2) [11].

More recently, the ectopic production of free βhCG in the absence of the alpha subunit has also been noted in many epithelial tumours [12-14]. In this context, βhCG production is usually a sign of aggressive disease and elevated levels of βhCG are strongly associated with poor prognosis [15,16]. This supports the hypothesis for βhCG having autocrine and paracrine growth factor qualities, which promote the growth and invasion of malignancy [17]. Initially it was thought that βhCG exerted these effects through increased cell proliferation but more recent work by Butler et al in 2000 [18] and Jankowska et al in 2008 [19] supports the theory that βhCG actually promotes cancer cell survival through inhibition of cancer cell apoptosis.

However, the exact mechanisms through which non-trophoblastic tumours produce βhCG remain uncertain. One possibility is that the pattern of expression of the six genes that code for βhCG is different in bladder carcinoma compared to normal urothelium. In particular, studies have demonstrated differential upregulation of the beta 3, 5 and 8 genes in cancerous bladder cells [20,21].

Expression and Excretion of ßhCG

HCG and/or its beta subunit are produced at low levels by the epithelia of many normal healthy tissues including, intestinal, urinary, respiratory, pituitary, testis and fallopian tubes. *In-vitro* studies by Iles et al. [22] showed that βhCG was excreted by four out of five 'normal' urothelial cell lines when they sampled their media. Using this excretory theory, urinary βhCG has been measured and also shown to be elevated in patients with bladder cancer. Although there were serious problems with correcting for dilution, it was possible to predict survival in bladder cancer patients based upon a raised urinary level [23].

The non-trophoblastic tissues above, including the urinary tract, almost exclusively express the βhCG encoded for by the beta 7 gene [24]. In contrast, βhCG expression in trophoblastic tissues is secondary to the transcription of either the beta 3, 5 or 8 gene [25]. This difference may be critical in the development of urothelial carcinoma.

Detectable βhCG in the serum of bladder cancer patients has been well documented; primarily in research performed in the 80s and 90s. Serum concentrations of βhCG in patients with bladder cancer have been shown to be raised, but there is a wide variation in the positivity observed. In 1994, Smith et al. [26] performed a prospective study of 163 patients being managed cystoscopically for disease across all stages and grades. They found that 10% of the patients had high levels of ßhCG but this had no correlation with survival, stage or grade.

In contrast, Dobrowlski [27] and Iles [28] have both observed increased levels of serum βhCG with increasing stage and grade of the disease. Here, Iles showed that 2/64 patients with locally confined bladder cancer had a raised βhCG compared with 16/21 patients with metastatic disease. Similarly, a more recent study by Venyo et al. [29] looked at 120 patients with bladder cancer being treated cystoscopically and measured their serum βhCG levels. They included two control groups: group A consisting of 30 patients with benign conditions (none of whom had raised βhCG levels), and group B that consisted of 70 patients with a history of TCC bladder but were currently disease free cystoscopically (of these only one had a raised βhCG). In the study group, 30% (36/120) of the patients had a raised serum ßhCG, and the levels increased through stage and grade, with 23% of superficial tumours and 47% of muscle invasive tumours being associated with a raised serum βhCG [29].

There are few studies looking at the immuno-histological expression of βhCG in bladder cancer and they show varying rates of expression of between 11% and 38% [29,30]. When the groups are broken down for stage and grade it becomes clear that expression levels increase in the poor prognosis groups. Studies show that between 18-63% of muscle invasive bladder cancer over-express βhCG [30,31], and this can be as high as 100% in metastatic disease [32]. One of these studies by Martin et al. [31] showed an over-expression rate of 29% in 100

patients, but also that the over-expressing tumours did not respond to radiotherapy.

Discussion

Currently there are no recommended biomarkers for use in the everyday clinical management of patients with Bladder Cancer. For such a common cancer, the lack of targeted therapies is surprising. The historical work summarised in this mini-review demonstrates βhCG to be an interesting marker with both potential prognostic and therapeutic applications.

There has been a lack of interest in βhCG over the last decade but there are a few exciting trials on the horizon. Perhaps the most promising use of βhCG in bladder cancer will be the result of an ongoing clinical trial looking at an anti-βhCG vaccine (CDX-1307) for treatment of bladder cancer, as an adjunct to current chemotherapy. In stage one of this trial the vaccine was given to patients with advanced and heavily pre-treated epithelial cancers (including colorectal, breast, pancreatic, and bladder) and it was found that the vaccine induced immune responses against βhCG even in the presence of high circulating levels of βhCG. There was also evidence of clinical impact on tumour growth (nine patients with stable disease for 2-18 months) [38]. Stage 2 clinical trials are now underway where the vaccine is being given to newly diagnosed, muscle invasive, βhCG-expressing bladder cancer, amenable to resection with curative intent [38].

It is not clear why the interest of the 1980s and 1990s waned but the authors feel that βhCG is a biomarker that has demonstrated potential and deserves further interest and research. ■

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