

REVIEW

Epidermal growth factor receptor and bladder cancer

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Muscle-invasive bladder cancer is a disease which causes significant morbidity and mortality. The two main forms of treatment for this disease include radical cystectomy and radical radiotherapy, but five year survival after treatment remains low at 40%. Many clinical and molecular risk factors have been shown to be associated with poor prognosis. One such factor is the expression of epidermal growth factor receptor (EGFR), which is overexpressed by many epithelial tumours, including bladder cancers. There are several methods of inhibiting the activity of EGFR and it may be that use of an anti-EGFR therapy, in combination with more conventional treatment, provides a method of improving the prognosis for muscle-invasive bladder cancer.

20%–40% of patients whose non-muscle-invasive tumours recur, progression to muscle-invasive bladder cancer occurs (see fig 2).^{11–13} Given the poor prognosis of muscle-invasive bladder cancer, much work has been undertaken to determine clinical and molecular prognostic markers predictive of progression in non-muscle-invasive bladder cancer. Clinical factors predictive of progression include presence of recurrent tumour at three month cystoscopy, increasing tumour stage and grade, increasing tumour size, carcinoma *in situ*, and tumour multifocality.^{7 8 13 13a} Many molecular markers predictive of tumour progression have been studied including deletion or expression of mutated forms of the tumour-suppressor genes, p53 and retinoblastoma, and expression of the proto-oncogene, *c-erbB-1*. The literature regarding these molecular markers is large and, in general, opinion is divided. p53 has been shown by some to be predictive of tumour progression,^{14 15} while other authors dispute this.^{16 17} Deletion or expression of a mutated form of the retinoblastoma gene is associated with tumour progression^{18 19} as is overexpression of the protein product of the *c-erbB-1* proto-oncogene, epidermal growth factor receptor (EGFR) (see box 1).^{20–22}

Bladder cancer is the fifth commonest male and seventh commonest female malignancy in England and Wales with an annual incidence of 10 500 cases and accounts for approximately 5000 deaths per annum.^{1–3} The term bladder cancer is used to describe collectively tumours of urinary bladder urothelial origin which exhibit diverse biological behaviour, ranging from relatively benign to highly malignant. Thus, bladder cancer can be without serious clinical consequences for the patient who has an isolated “superficial” bladder tumour and dies many years later of an unrelated cause, or it can be a lethal disease resulting in death a short time after presentation. Eighty per cent of bladder cancers are “superficial” at presentation in that they have not invaded into the detrusor muscle (Ta, T1 tumours). The remaining 20% are “muscle-invasive”, extending through the detrusor muscle (T2–4 tumours) and such tumours carry a much graver prognosis (see fig 1).

The natural history of bladder cancer is dependent on the stage and grade of the initial tumour. For patients whose initial tumour is non-muscle-invasive the prognosis is good. At five years, 50% of patients will remain recurrence free, 20% will have experienced one recurrence, and the remaining 30% will have had multiple recurrences.⁴ Of those patients who experience recurrence, 50%–70% of recurrent tumours are of similar histological grade and stage as the primary tumour.^{4 5} Factors predictive of tumour recurrence include presence of recurrent tumour at the three month check cystoscopy, increasing tumour stage and grade, increasing tumour size, tumour multifocality, presence of carcinoma *in situ*, and positive urine cytology (see box 1).^{6–10} In

The treatment of bladder cancer is dependent on the presenting tumour's grade and stage. Non-muscle-invasive tumours are treated by transurethral resection with or without subsequent intravesical chemotherapy or immunotherapy. In view of its poorer prognosis, the treatment of muscle-invasive tumours is more radical. The two main therapeutic options available for tumours confined to the bladder are radical cystectomy or radical radiotherapy, but the five year survival after either regimen remains poor at 40%.^{23–27} The prognosis for patients with muscle-invasive bladder cancer is dependent on a number of clinical factors. Increasing tumour stage and grade, solid tumour morphology, low haemoglobin levels, the presence of positive pelvic lymph nodes, and the presence of ureteric obstruction are associated with a subsequent poor prognosis.^{26 28–31}

The challenge to the modern urologist is twofold: firstly, to detect the small but significant proportion of patients with non-muscle-invasive bladder cancer who will progress to muscle-invasive disease and secondly, to improve the prognosis of patients with muscle-invasive bladder cancer.

Abbreviations: EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; HB-EGF, heparin-binding EGF-like factor; TGF- α , transforming growth factor-alpha

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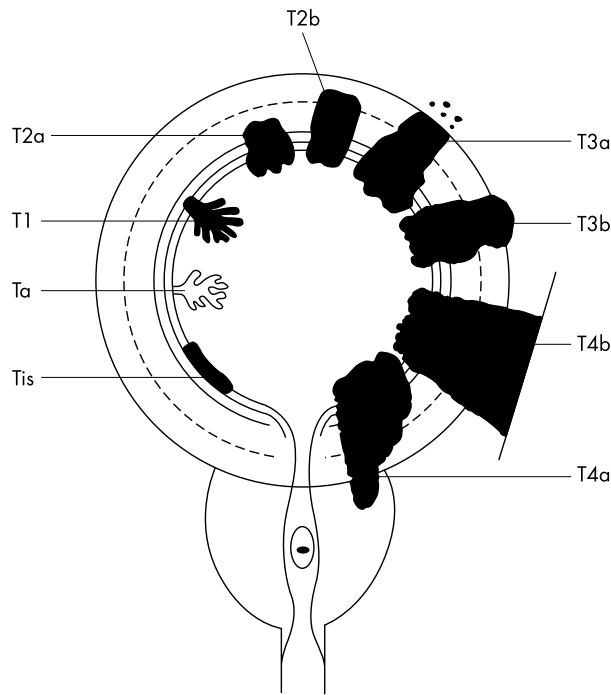


Figure 1 T staging of bladder cancer. Tis, carcinoma *in situ*; Ta, tumour involves mucosa only; T1, tumour invades through lamina propria; T2a, tumour invades into superficial detrusor muscle; T2b, tumour invades into deep detrusor muscle; T3a, tumour microscopically invades perivesical tissue; T3b, tumour macroscopically invades perivesical tissue and forms extravesical mass; T4a, tumour invading prostate/uterus/vagina; T4b, tumour fixed to pelvic wall.

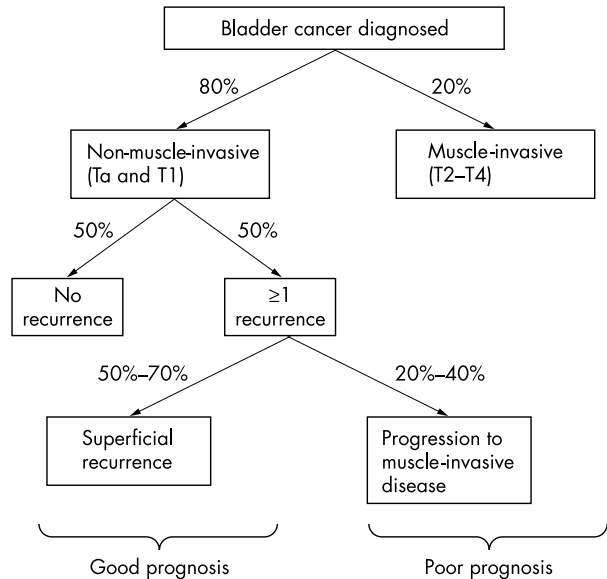


Figure 2 Natural history of bladder cancer.

EPIDERMAL GROWTH FACTOR RECEPTOR FAMILY

The epidermal growth factor receptor (EGFR) is a member of the tyrosine kinase receptor family, a group of receptors which are all encoded by the *c-erbB* oncogenes. There are four known *c-erbB* oncogenes whose transcription produces a variety of protein products that play a physiological role in coordinated cell growth and tissue repair (see fig 3). Pathological expression of these proto-oncogenes is associated with the loss of coordination of cell growth that typifies malignancy. For example, the overexpression of *c-erbB-2* has been

Box 1: Factors predictive of superficial tumour recurrence and progression

- Recurrent tumour at three month check cystoscopy.
- Increasing tumour stage and grade.
- Increasing tumour size.
- Tumour multifocality.
- Presence of carcinoma *in situ* (recurrence, progression).
- Positive urine cytology (recurrence).
- Deletion/mutation of retinoblastoma gene (progression).
- Expression of *c-erbB-1/EGFR* (progression).
- ?Expression of p53 (progression).

Box 2: Factors predictive of poor prognosis for muscle-invasive bladder cancer

- Increasing tumour stage and grade.
- Solid tumour morphology.
- Low haemoglobin levels.
- Ureteric obstruction.

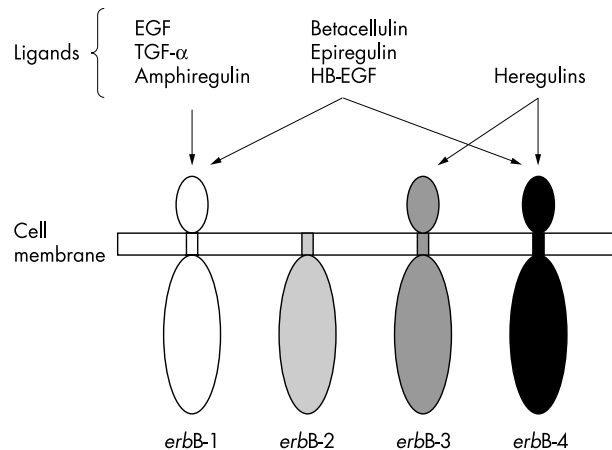


Figure 3 The *c-erbB* family of receptors and their activating ligands. EGF, epidermal growth factor; HB-EGF, heparin-binding EGF-like factor; TGF- α , transforming growth factor-alpha.

associated with poor prognosis in patients with advanced breast cancer.³² However, in patients with bladder cancer, overexpression of *c-erbB-2* has less prognostic significance.^{33, 34} Numerous studies have determined that expression of the *c-erbB-1* proto-oncogene is associated with poor prognosis in patients with bladder cancer.^{20, 22, 35-37}

Epidermal growth factor was first identified and purified from the submaxillary glands of mice by Cohen in the 1960s, in his search for nerve stimulating growth factors.³⁸ It was not, however, until 1984 that the EGFR was sequenced and cloned on chromosome 7.^{39, 40} EGFR is the protein product of the *c-erbB-1* proto-oncogene and is a 170 kDa protein that consists of three distinct structural parts (see fig 4). The extracellular component forms the ligand binding region that is activated by one of several ligands (epidermal growth factor (EGF), transforming growth factor-alpha (TGF- α), amphiregulin, betacellulin, heparin-binding EGF-like factor (HB-EGF) and epiregulin) (see fig 3).⁴¹ The transmembrane component is a short single stretch of 27 amino acids that traverses the cell membrane to reach the intracellular component of the receptor. The intracellular component consists of two separate domains; adjacent to the cell membrane is a catalytic domain with tyrosine kinase activity and contiguous with this is the autophosphorylation domain.⁴² Activation of EGFR by one of its respective ligands leads to formation of both homodimers

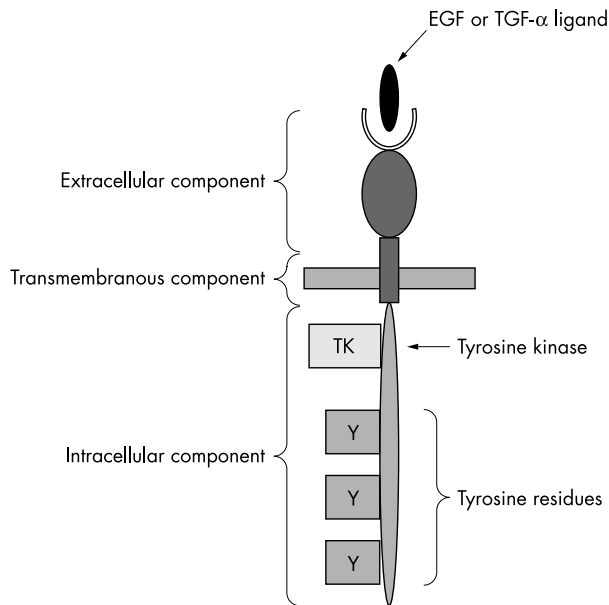


Figure 4 Epidermal growth factor receptor.

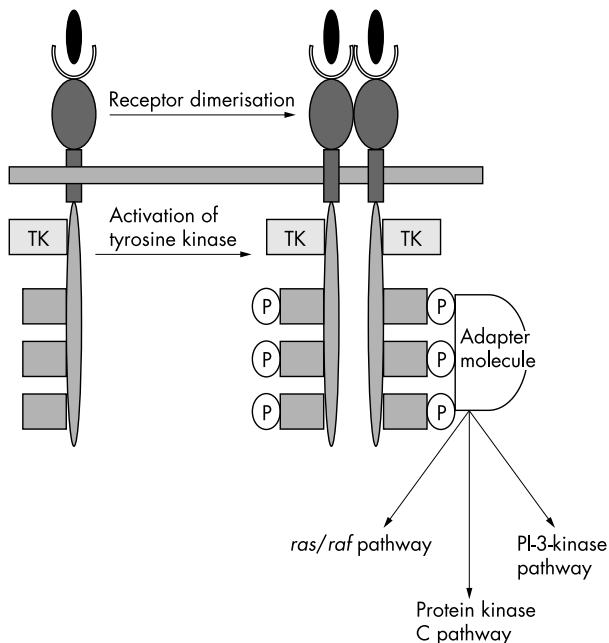


Figure 5 Activation of the EGFR. PI-3-K, phosphatidylinositol-3-kinase.

(with other EGFR) and heterodimers (with other members of the *c-erbB* family).^{42,43} This conformational change leads to phosphorylation of the tyrosine residues located within the autophosphorylation domain. These phosphotyrosines in turn phosphorylate other intracellular proteins that contain *src* homologous domains (SH2 and SH3). These intracellular proteins include phospholipase C γ , *ras* associated GTPase activating protein and phosphatidylinositol-3-kinase.⁴⁴⁻⁴⁶ Phosphorylation of these intracellular proteins stimulates the *ras/raf*, phosphatidylinositol-3-kinase and protein kinase C pathways, which ultimately lead to increased nuclear transcription and subsequent cellular proliferation (see fig 5).

EGFR AND BLADDER CANCER

As outlined above, pathological expression of EGFR leads to uncontrolled cell proliferation. It also results in increased ang-

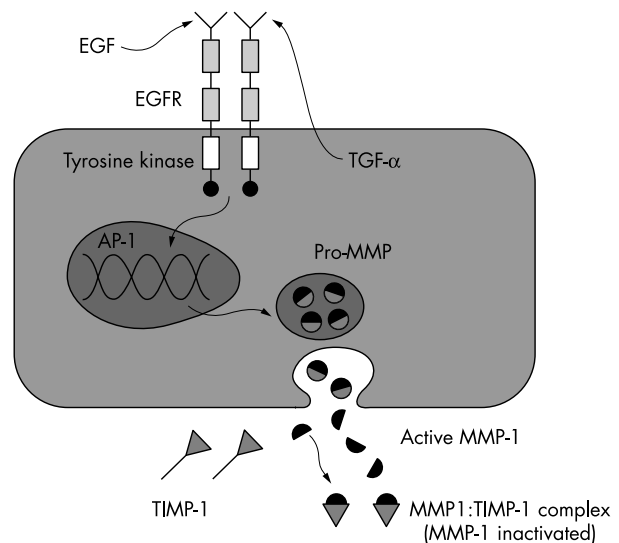


Figure 6 Potential mechanism linking EGFR to invasion and metastasis. AP-1, activator protein-1; MMP, matrix metalloproteinase; TGF- α , transforming growth factor-alpha; TIMP, tissue inhibitor of metalloproteinase.

Box 3: Incidence of EGFR positivity in epithelial tumours

- Non-small cell lung cancer: 40%–80%.
- Colorectal cancer: 25%–77%.
- Prostate cancer: 40%.
- Ovarian cancer: 35%–70%.
- Advanced gastric cancer: 33%.
- Pancreatic cancer: 30%–50%.
- Breast cancer: 15%–30%.
- Bladder cancer: 50%.

iogenesis and reduced apoptosis, processes necessary for continuing malignant growth.⁴¹ EGFR is known to be overexpressed by many epithelial tumours including non-small cell lung, colorectal, gastric, pancreatic, ovarian, and breast cancers (see box 3).³⁵ Overexpression of EGFR in bladder cancer has been widely reported,^{20,22,36,37} and several studies have shown EGFR positivity to be associated with high tumour stage, tumour progression, and poor clinical outcome.^{20,22,47} The mechanism by which EGFR expression is associated with poor prognosis is not entirely clear, although there is some evidence linking EGFR stimulated activation of activator protein-1 transcription factor with induction of matrix metalloproteinase activity (see fig 6).⁴⁸

ACTIVATION OF EGFR BY RADIOTHERAPY

Recent work has shown that EGFR activity is stimulated by ionising radiation (radiotherapy).⁴⁹⁻⁵¹ This upregulation of EGFR activity is effected by the autocrine activity of radiation-induced TGF- α release.⁵² The upregulation of EGFR activity via radiation may lead to cellular proliferation. Such stimulation of cellular proliferation by radiotherapy may allow repopulation of cells to occur between fractions of radiotherapy accounting for the radioresistance seen in certain tumours. In vivo work using malignant glioma cells by Lammering *et al* has elegantly shown that inhibition of EGFR by transfection of a dominant-negative EGFR (inactive EGFR) and subsequent application of irradiation leads to a 1.8-fold tumour radiosensitisation effect.⁵³ Current work at the University of Leicester is assessing the response of muscle-invasive bladder cancers to radiotherapy, in relation to a tumour's EGFR status.

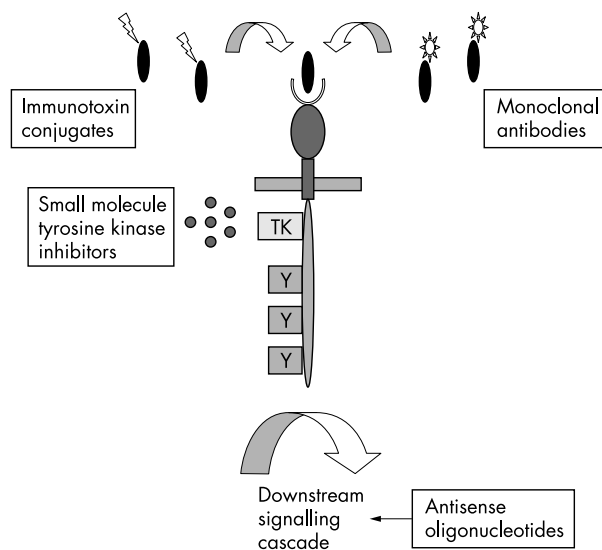


Figure 7 Methods of inhibiting EGFR activity.

MANIPULATION OF EGFR ACTIVITY

Given that EGFR overexpression is associated with poor prognosis and possible poor response to treatment, it follows that inhibition of EGFR activity may be a way of improving the prognosis for patients with bladder cancer. There are several ways in which EGFR activity can be inhibited including use of small molecule tyrosine kinase inhibitors (for example, ZD 1839, Astra Zeneca, Macclesfield, UK), monoclonal antibodies against EGFR (for example, IMC-C225, ImClone, New York, USA), immunotoxin conjugates, and antisense oligonucleotides (see fig 7).⁴¹ To date the most studied methods of inhibition are small molecule tyrosine kinase inhibitors and monoclonal antibodies.

ZD 1839 is administered orally and has been shown to be well tolerated in phase I testing involving patients with a range of EGFR expressing malignancies (including breast, prostate, colorectal, and head and neck cancers).⁵⁴ IMC-C225 is administered intravenously and has also been found to be well tolerated in phase I testing in patients with breast, bladder, prostate, and colorectal cancer.⁵⁵ Both these therapies have been shown to have additive effects *in vitro* when used in conjunction with other conventional chemotherapeutic and radiotherapeutic treatments.^{55–57} ZD 1839 is now being tested in a multicentre phase III trial in conjunction with carboplatin/paclitaxel in the treatment of advanced non-small cell lung cancer and IMC-C225 has entered phase III testing in the treatment of head and neck cancer.

As well as acting to improve treatment of primary tumours, the potential exists for anti-EGFR therapies to treat metastatic disease. Work by Sainsbury *et al* has shown that, in breast cancer, metastatic lesions are more likely to express EGFR than primary tumours.⁵⁸ Work by Bue *et al* in bladder cancer metastases has shown a positive correlation between the EGFR status of primary bladder tumours and associated metastases.⁵⁹ By targeting therapies at inhibition of EGFR not only would it be possible to attempt to improve prognosis in the treatment of primary EGFR expressing tumours but it may also be possible to selectively target EGFR expressing metastases, irrespective of the primary tumour's EGFR status.

CONCLUSION

Bladder cancer is a prevalent disease that causes substantial morbidity and mortality. Despite the continued refinement of surgical techniques—namely, radical cystectomy—the prognosis of muscle-invasive bladder cancer has remained unchanged for the past 30 years with five year survival

Box 4: Key references

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remaining disappointingly low at 40%. Increased understanding of the molecular basis of bladder cancer progression, recurrence, and metastasis has led to identification of EGFR as a significant prognosticator in both non-muscle-invasive and muscle-invasive bladder cancer. The knowledge that EGFR expressing tumours are associated with poor prognosis has led to the development of several strategies to inhibit EGFR activity. Phase I and II testing of anti-EGFR therapies have shown promising results and the results of phase III testing of small molecule tyrosine kinase inhibitors and anti-EGFR monoclonal antibodies, either as monotherapies, or in combination with more conventional chemotherapeutic and radiotherapeutic treatment regimens are eagerly awaited. Pending the outcome of these studies subsequent testing of anti-EGFR therapies in patients with bladder cancer may provide evidence of a realistic treatment option to improve the prognosis for these patients.

MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AT END OF REFERENCES)

Q1. Epidermal growth factor receptor is overexpressed by the following tumours:

- (A) Adenocarcinoma of the breast
- (B) Osteosarcoma
- (C) Squamous cell carcinoma of the head and neck
- (D) Leiomyoma

Q2. The following statements are true with regard to non-muscle-invasive bladder cancer:

- (A) Progression occurs in 50%–70% of cases
- (B) Increasing tumour grade and stage are predictive of recurrence
- (C) Overexpression of *c-erbB-2* is a risk factor for progression
- (D) Multifocality is a risk factor for tumour recurrence

Q3. Deletion/mutation of the following genes is associated with non-muscle-invasive tumour progression:

- (A) Retinoblastoma
- (B) *c-erbB-1*
- (C) *H-ras*
- (D) *c-erbB-2*

Q4. The following are risk factors for non-muscle-invasive tumour recurrence:

- (A) Increasing age
- (B) Low haemoglobin levels

- (C) High tumour grade
 (D) Previous tumour recurrence
 Q5. Epidermal growth factor receptor:
 (A) Is encoded on chromosome 17
 (B) Can form heterodimers with other members of the *c-erbB* receptor family
 (C) Stimulation results in cellular proliferation
 (D) Is frequently over expressed in bladder cancer
 Q6. Survival from muscle-invasive bladder cancer is worse in:
 (A) Patients undergoing radical radiotherapy as opposed to radical cystectomy
 (B) Patients with high tumour stage
 (C) Patients with ureteric obstruction
 (D) Older patients

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ANSWERS

- Q1. (A) T, (B) F, (C) T, (D) F. Q2. (A) F, (B) T, (C) F, (D) T. Q3. (A) T, (B) F, (C) F, (D) F. Q 4. (A) F, (B) F, (C) T, (D) T. Q5. (A) F, (B) T, (C) T, (D) T. Q6. (A) F, (B) T, (C) T, (D) F.

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