Etiopathogenesis of bladder cancer. Risk factors, genetic aspects and novel diagnosis biomarkers

1,2,3 Anamaria Truța, 4 George Saraci, 5 Tudor-Adrian Hodor-Popon, 6 Liviu Ghervan, 1 Ioan V. Pop

1 Department of Medical Genetics, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; 2 Research Center for Functional Genomics Biomedicine and Translational Medicine, "Iuliu Hatieganu" University of Medicine Pharmacy, Cluj-Napoca, Romania; 3 Oncology Institute, Cluj-Napoca, Romania; 4 Department of Internal Medicine “Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania; 5 Department of Urology-Robotic Surgery, Clinical Municipal Hospital, Cluj-Napoca, Romania; 6 Clinical Institute of Urology and Kidney Transplant, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca.

Abstract. Bladder cancer is a complex pathologic process with multifaceted etiology and etiopatogenesis dependent of various factors: chemical carcinogens (smoking, professional exposure, artificial sweeteners, pelvic radiation, diet, and industrial carcinogens), drug abuse, chronic treatments with antibiotics and cyclofosfamide, menopausal hormone therapy). Genetic factors (genetic polymorphisms, miRNA) are involved in bladder cancer etiopathogenesis, evolution, prognosis, response to specific therapy or survival rates. Dietary factors are mentioned as part of bladder carcinogenesis (meat consumption, total fluids intake, vegetables, artificial sweeteners) as well as various disorders in patient’s medical history (chronic infection and inflammation of urinary bladder, schistosomiasis, chronic lithiasis, catheterism, HPV infection, pelvic radiation). Family history of cancers (bladder and kidney cancers, cervix cancers) along with bladder chronic inflammations and bladder dysplasia are among risk factors. Genetic component is very important in bladder carcinogenesis (XPC, ERCC2 and ERCC5 genetic variants, NRF2 and NRF2 target genes, p53 and Rab oncogene). Current paper focuses on the pathogenesis of bladder cancer stressing upon modern genetic markers and questionnaires applied to risk population are designed to use in early stage using clinical and genetic laboratory parameters and find new diagnostic strategies. These new biomarkers (miRNA, genetic polymorphisms) might represent useful tools in developing new non invasive tumoral biomarkers in bladder malignancies. These new tumoral non invasive biomarkers (miRNA, genetic polymorphisms) might represent useful tools in developing new diagnostic strategies, new therapeutic options, novel techniques in monitoring bladder cancer evolution after surgical treatment or in monitoring non muscle invasive cancers, but also for screening programmes applied on risk population and significantly decrease bladder cancer incidence worldwide. Screening and prophylactic programmes which aim to diagnose diseases in early stage using clinical and genetic laboratory parameters and questionnaires applied to risk population are designed to be available worldwide after clinical validation. miRNA can be part of screening programmes after clinical validation and will offer opportunity of more efficient non invasive screening programmes easily accepted by risk population than current screening programmes based on invasive procedures (cystoscopy, biopsy). The new non invasive tumoral biomarkers might be included in new precise therapeutic strategies. The aim is to optimize therapy response, minimize side effects of oncologic therapies but also to increase life quality of oncologic patients and to reduce recurrences rates of bladder carcinoma (Ye et al 2014; Goodison et al 2013). Describing the complete etiopathogenesis in bladder cancer and its complex pathologic mechanisms by altering control processes and DNA repair mechanisms and also the disorders which underlay bladder cancer development will make us understand better this pathology and find new diagnostic strategies. All these findings can lead us to early diagnosis and real rates of positive diagnosis. Many cases of bladder cancer are not diagnosed correctly or in early stages, being often confused with chronic inflammation, fibrosis, other bladder pathologies or prostate pathology due to urinary tract contiguity and similar symptoms (polyuria, pollakiuria, hematuria, abdominal pain) (Urquidi et al 2012).
Epidemiology. Risk factors. Etiopathogenesis

Bladder cancer is the most common malignancy of the urinary tract with the incidence being four times higher in men than in women (Schned et al. 2012). Caucasians have higher incidence of bladder cancer but the reason is not known yet. Development of urothelial carcinoma is also related to age with a 70 – 73 years median age of diagnosis (Walker et al. 2014). North America leads in incidence while lower incidence is reported in Japan and Finland. It will be interesting to prove if geographic distribution is dependent on environmental risk factors, diet, occupational exposure or genetic differences (Working Groups 2014).

Table 1. Bladder cancer incidence (Walker et al. 2014)

<table>
<thead>
<tr>
<th>Bladder cancer incidence (Men ≥ 85 years old)</th>
<th>Women ≥85 years old</th>
<th>Women ≤85 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>142 / 100.000</td>
<td>74/100.000</td>
<td>33/100.000</td>
</tr>
</tbody>
</table>

Table 2. Bladder cancer incidence and mortality in US 2015 (www.cancer.org)

<table>
<thead>
<tr>
<th>Bladder cancer statistics in 2015</th>
<th>Number of cases</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>incidence</td>
<td>74</td>
<td>56.32</td>
<td>17.68</td>
</tr>
<tr>
<td>mortality</td>
<td>16</td>
<td>11.5</td>
<td>4490</td>
</tr>
</tbody>
</table>

Intrafamilial clusters (perinatal mother-to-infant or early horizontal transmission) have been reported in bladder cancer pathology and recent studies suggested the role of genetic polymorphisms in bladder carcinogenesis. This hypothesis opens new research pathways in finding new diagnostic biomarkers in bladder cancer but also in predicting bladder cancer evolution, recurrence, prognosis and define new therapeutic solutions according to molecular profile of bladder tumors (Hemminki et al. 2011). Family and personal clinical history of bladder cancer is a well known risk factor in bladder cancer etiopathogenesis and susceptibility. New data emerged on the influence of family history tumours rather than bladder cancer. Family history of bladder tumours influenced survival rates, prognosis and evolution (Hemminki et al. 2011; Blaveri et al. 2005).

Many genetic polymorphisms are identified in bladder cancer etiopathogenesis which influence bladder tumors susceptibility, prognosis or therapy response in oncologic patients (Reszka et al. 2014). Infectious and inflammatory disorders. Neutrophils, macrophages, lymphocytes promote tumor development and rapid progression of carcinogenic process. Neutrophils are responsible of secretion of neutrophil peptides 1-3 which promotes carcinogenesis. Primary response of macrophages is induced by pro inflammatory cytokines: IL 6 and TNFα (Thompson et al. 2014). All these mechanisms explain part of bladder carcinogenesis, correlation with chronic inflammatory disorders and treatment or
cytokine-modified tumor effects (Desai et al 2014). Cytokines levels are correlated with incidence, recurrences, therapy response, evolution, some genetic polymorphisms, survival rates and response at BCG therapy. Lymphotoxin β receptor is up-regulated in bladder cancer via activation of Nuclear Factor - κB, then NF –κ B can explain part of pathogenesis. NF –κB explains correlation between those two bladder pathologies. Levels of proteins are correlated with histologic grade, clinical stage, lymph node metastasis. Consequently they are possible candidates in non invasive tumoral biomarker diagnosis of bladder cancers (Thompson et al 2014; Shen et al 2014; Luo et al 1999; Kamat et al 2007).

There are new proven correlation between urogenital schistosomiasis and bladder carcinogenesis. There is no molecular mechanism described which links schistosomiasis to bladder carcinogenesis. New experimental studies on animal models must prove molecular mechanisms induced by Schistosoma hematobium in bladder carcinogenesis (Fu et al 2012). The parasite induces inflammation, fibrosis, dysplasia and increases transcription of collagen genes COL 17A1, but also metalloproteinases 9, 10 and 13. TIMP 1 (tissue inhibitor of metalloproteinase) is also part of fibrotic and displastic process in bladder pathology. Other genes are inhibited by Schistosoma infection: COL 6 A3, COL8A2, COL4A5, COL3A1 (Honeycutt et al 2014; Botelho et al 2011).

New clinical researches revealed the correlation between bladder cancer and diabetes mellitus, actually between diabetic patients under pioglitazone therapy and bladder cancer. γ -peroxisome-proliferator receptor (PPARγ) is detected in normal urothelium but over expressed in bladder cancers and represent part of differentiation and tumor proliferation. This new findings reveal importance of developing screening tests in type 2 diabetes patients treated with Pioglitazone as part of bladder cancer prevention (Mylona et al 2009). Neurogenic bladder, urinary lithiasis, bladder anomalies (bladder diverticula), along with invasion of colorectal carcinoma are cited among risk factors (Chung et al 2013). It will be important to reveal pioglitazone’s side effects and metabolic pathways in order to avoid next generation treatments with similar carcinogenesis risks.

In bladder cancer smoking is correlated with number of cigarettes, duration of smoking, intensity, type of administration. It was proven to be main part of bladder carcinogenetic process and it was also correlated with poor prognosis, high recurrence rates, poor response to therapy and low survival rates. Smoking cessation improves quality of life in oncologic patients while smoking was correlated with bladder cancer recurrences (Sosnowski et al 2014).

Chemical carcinogenesis. It was proven that MBT (mercapto benzothiazole), PBN (phenyl - α naphthylamine), ortho-toluidine, acroleine or benzidine are part of bladder carcinogenesis (Sorahan et al 2008). Exposure to arsenic in drinking water, aromatic amines , 4 ‘4 ‘methylenebis 2- chloroaniline are involved in bladder cancer etiopathogenesis as well as chemical carcinogens derived from smoking like benzidine, nitrosamine or acroleine. Exposure to hair dyes is also part of bladder carcinogenesis, benzidine proved to be an important risk factor (Xiang et al 2007). Expression of mutant p53 protein after benzidine exposure was studied by immuno PCR assay in order to prove its carcinogenetic role in bladder malignancies. Ifosfamide caused often hemorrhagic recurrent cystitis through its metabolite acroleine and this mechanism could explain bladder carcinogenesis via preneoplastic disorders induced mainly by COX 2 inhibition (Letasiova et al 2012; Macedo et al 2011). Diet. It seems that higher fluid intake per day might reduce bladder cancer incidence but proofs are inconsistent and need more trials (Bai et al 2014). Alcohol consumption and bladder malignancies correlation are still inconsistent and needs molecular mechanisms to explain pre neoplastic bladder disorders (Kim et
There was a positive correlation between coffee consumption and bladder cancer in studies adjusted for sex, age and smoking status. Bladder cancer risk is 80% increased in coffee drinkers of more than 10 cups per day versus non coffee drinkers (Sala et al 2000). Green tea consumption was not associated with bladder carcinogenesis and had anti-inflammatory effect on urothelium (Henriques et al 2014). Meat consumption is associated with increased risk of various human malignancies, including bladder cancer while fruits and vegetables, especially cruciferous might have protective effects. Soy is rich in isoflavones like genistein and daidzein and is correlated with lower incidence of bladder cancers. Vitamins A and E and selenium have protective effects in bladder cancer as well as multivitamins combinations (Wennersten et al 2014).

### Genetic polymorphism and diagnostic biomarkers

**CHEK2** - is a suppressor gene localized on chromosome 2 which encodes protein CHEK2 involved in DNA repair processes functioning as a suppressor of carcinogenesis in bladder cancer. Main genetic polymorphisms of CHEK2 gene involved in bladder cancer are: IVS 2, IG= , 1100 del C, del 5395, I 157 T (Liu et al 2014). CYP1B1 - is localized on chromosome p22-21 and encodes a protein made of 543 aminoaids which controls estradiol and xenobiotics metabolic pathways. Banaszkiewicz et al (2013) described Arg4Gli (m1 ), Ala119Ser (m2- in SRS 1), Leu432Val (m3), Asn453Ser (m4 ) as main genetic polymorphisms involved in bladder carcinogenesis (Jiang et al 2014; Scheffler et al 2014). HPV infection is also mentioned as part of etiopathogenesis in various malignant tumors. It contains 2 oncoproteins: E6 and E7 which create complex interactions with p53 protein and its tumoral suppression function (Banaszkiewicz et al 2014). CYP1B1- is localized on chromosome p22-21 and encodes a protein made of 543 aminoaids which controls estradiol and xenobiotics metabolic pathways. Banaszkiewicz et al (2013) described Arg4Gli (m1 ), Ala119Ser (m2- in SRS 1), Leu432Val (m3), Asn453Ser (m4 ) as main genetic polymorphisms involved in bladder carcinogenesis (Jiang et al 2014; Scheffler et al 2014). HPV infection is also mentioned as part of etiopathogenesis in various malignant tumors. It contains 2 oncoproteins: E6 and E7 which create complex interactions with p53 protein and its tumoral suppression function (Banaszkiewicz et al 2014). CYP1B1- is localized on chromosome p22-21 and encodes a protein made of 543 aminoaids which controls estradiol and xenobiotics metabolic pathways. Banaszkiewicz et al (2013) described Arg4Gli (m1 ), Ala119Ser (m2- in SRS 1), Leu432Val (m3), Asn453Ser (m4 ) as main genetic polymorphisms involved in bladder carcinogenesis (Jiang et al 2014; Scheffler et al 2014). HPV infection is also mentioned as part of etiopathogenesis in various malignant tumors. It contains 2 oncoproteins: E6 and E7 which create complex interactions with p53 protein and its tumoral suppression function (Banaszkiewicz et al 2014).

Recent genetic research studies proved that IL – 1RN and IL – 4 gene polymorphisms are also important genetic markers of susceptibility to bladder cancer. Studies have the role to define precisely involvement of these genetic biomarkers in etiopathogenesis, diagnosis, evolution, recurrences and use these tumoral non-invasive genetic biomarkers in positive diagnosis of cancer. This will allow us to get an early diagnosis, improve life quality and survival rates, decrease number of recurrences and define precise therapy in oncology (Zhang et al 2014). Recent meta-analysis studied relation between MMP (matrix metalloproteinase) and bladder cancer. Results are still contradictory and will open new perspectives in proving complex etiopathogenesis in bladder cancer: genetic, environment factors, dys, industrial and chemical carcinogenetic factors. Studies of MMP-I-1607 1G/2G , MMP -2-1306 and MMP -9-1562 C/T and their role in bladder cancer have already proven the correlation between MMP –I-1607 1G/2G genetic polymorphism and bladder cancer but only in recessive models and a significant correlation between MMP -2-1306 C/T in homozygote models of bladder cancer. There are no correlation between MMP -9-1562C/T and bladder cancer (Chu et al 2013). Case control studies aiming to complete etiopathogenesis proved that serum levels of MMP 9 and MMP 7 are higher in patients with bladder cancer than in controls, while TIMP -1 (tissue inhibitor of matrix metalloproteinase) is lower in patients diagnosed with bladder cancer (Kim et al 2013). Other recent researches tried to define correlation between Lys939Glu polymorphism of xeroderma pigmentosum group XPC and bladder cancer susceptibility. Based on large meta-analysis studies results reported Lys939Glu as important factor in bladder cancer in homozygous models (Zhang et al 2014). MDM 2 SNP 309 T > G genetic polymorphisms are also involved. New meta-analysis proved that genotype for MDM 2 309 T > G is associated with important risk of bladder cancer (Shen et al 2012). MPM 8 is surely not correlated with higher risk of bladder cancer in Caucasian population (Zhang et al 2014; Wang et al 2012; Vasudevan et al 2011). MiRNAs are small non coding molecules with an approximately 22 nucleotides which act as post transcriptional regulators of gene expression. They are important in carcinogenesis, tumor progression, evolution, metastasis and prognosis (Xiu et al 2014). They might represent important diagnostic biomarkers in various oncologic disorders but also a prognosis biomarker in evaluating tumor progression, recurrences or metastasis. They could be useful parameters in developing new therapeutic strategies in oncology by selecting individualized therapy in order to optimize response to therapy, obtain better response, minimize side effects and above all increase life quality of oncologic patients (Zhang et al 2014; Vasudevan et al 2011; Uppal et al 2014).
miRNA-133 expression proved to be altered in urologic malignancies, including bladder carcinoma. Aberrations in miR expression appeared in different forms for muscle invasive bladder cancer and non muscle invasive type. This fact will define accurate tumoral biomarkers in bladder cancer which can predict clinical features, histologic type, evolution and also prognosis (Noguchi et al 2013). MiRNA-133a and miRNA-133b are located both on the same cistronic unit of chromosome 18 and are important biomarkers for various human malignancies: bladder cancer, pancreatic ductal carcinoma, hepatocellular carcinoma, esophageal carcinoma, carcinoma of the tongue. Experimental studies which used bladder cancer xenografts in mouse models confirmed that miR-133 and miR-218 effectively suppressed bladder cancer evolution (Zhao et al 2013). MIR-99a, also evaluated as potential tumoral diagnostic cancer biomarker was significantly down regulated in bladder cancer tissues. Even in low expression in bladder carcinoma it was correlated with aggressive phenotypes, rapid progression and poor prognosis albeit some studies suggested that miRNA 99a inhibits bladder cancer cell growth by arresting G1/S transition (Wu et al 2014). MiRNA200c is part of bladder carcinogenesis, correlated with disease progression and poor prognosis in T1 bladder cancer (Ichimi et al 2009). MIR-200c/141 cluster was upregulated in bladder urothelial carcinoma versus normal bladder urothelium and its expression was reduced in invasive bladder cancer versus non invasive bladder tumour. It functions as a promoter of hypermethylation mechanism which can define bladder carcinogenesis (Shan et al 2013; Feng et al 2013). It also controls dysplastic process and sensitivity to EGFR therapy. MiRNA-200c expression includes EGFI (novel receptor for EGFR) which can lead to new therapy protocols in bladder cancers and optimize therapy response using well defined etiopathogenetic pathways (Rosenberg et al 2013). MiRNA-200c is also correlated with bladder cancer invasion-metastatic process. It is part of other carcinogenetic processes in colorectal, lung, endometrial carcinoma, hepatocellular carcinoma, epithelial ovarian cancer, pancreatic carcinoma, or pre neoplastic disorders like Barrett esophagus. It can be used as a poor prognosis biomarker and predicts poor response to specific chemotherapy. MiR-200 family, miR – 155, miR-192 and miR-209 are depressed in bladder cancer (Shan et al 2013; Wang et al 2012). MiR 200 c, 200 b, 30a, 30 e are also related to cancer progression and poor prognosis (Baffa et al 2009). TNM bladder cancer classification evaluates tumour size and depth of invasion (T), number and localization of lymphnodes (N) and loco-regional or distance metastasis (M); for stage 0 miRNA seems to have a high impact.

The miRNA-214 levels were significantly higher in bladder smooth muscle of invasive bladder cancer than in controls and can be used in bladder cancer initial diagnostic and recurrences (Kim et al 2013). Together with miRNA-639 can lead to early diagnosis and individualized therapy according to molecular profile (Scheffer et al 2014). Four miRNAs are significantly expressed in muscle-invasive bladder cancer versus non muscle invasive bladder cancer: miR-214, -205, -141, -199a -3p (Feng et al 2014; Ratert et al 2013).

MIR-210 is a typical hypoxic micro RNA expressed in hypoxic conditions in HIF-dependent mechanism. miRNA 210 is upregulated in peritoneal macrophages treated with LPS so it may have regulatory role in LPS/TLR4 signaling. MIR 210 overexpression can inhibit TLR 4 induced secretion of proinflammatory cytokines IL6 and TNF, targeting directly TNF -k -B1 (Li et al 2014; Catto et al 2011). It is a poentially negative feed back regulator in LPS / TLR 4 signaling pathways and its role in urologic malignancies was proved. MIR- 210, - 25b, -146, -55 are controlled by inflammatory signals from cells- part of functionally innate or adaptive immune responses or oncogenic signals (Catto et al 2011; Tili et al 2013; Feng et al 2014). Studying proliferative capacity induced by MIR210 in carcinogenesis, various mechanisms are mentioned. They include production of growth factors ligands, stimulation of cell proliferation in tumors and disruption of negative feed back which attenuates proliferative signaling (Odisho et al 2013).
Table 5. Stage 0 bladder cancer, a prominent application for miRNA as diagnostic tool (AJCC 2010)

<table>
<thead>
<tr>
<th>miRNA</th>
<th>miRNA’s value</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diagnostic</td>
<td>Prognostic</td>
</tr>
<tr>
<td>miRNA145</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>miRNA133</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>miRNA128</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>miRNA99a</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>miRNA200c</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>miRNA200c/141</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>miRNA205</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>miRNA30a</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>miRNA16</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>miRNA200b</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>miRNA210</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>miRNA46</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>miRNA192</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>miRNA34a</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>miRNA576-3p</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>miRNA 133b</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>miRNA 576-3p</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>miRNA451</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>miRNA451</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>miRNA 133b</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>miRNA 96</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>miRNA100</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>miRNA 137</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>miRNA 137</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

Although risk factors in bladder cancer are about the same as they were 20 years ago, the mechanism and their interactions reveal new pathways along with genetic aspects, making this clinical entity a multifaceted issue. Current prognostic factors of bladder cancer progression and recurrence rates are represented by: tumor grade, stage, size, number of bladder tumors, multifocality, associated in situ carcinoma. All those parameters used in EORTC bladder cancer scale cannot reflect clinical outcome of oncologic patients or atypical clinical picture in bladder cancer pathology. Research studies try to identify
new prognostic parameters which can explain etiopathogenesis but also predict prognosis and represent useful tools in bladder cancer individualized therapy. Already proven with important role in bladder carcinogenesis are miRNA-20a,-106b,-141,205,-200a, along with down regulated in bladder cancer pathology: miRNA-130 a, 139-5p, 145, -199a. Nowadays bladder cancer is diagnosed by cystoscopic examination with cytologic and histologic tests. It is easy to understand that we need new diagnostic tools like tumoral non invasive biomarkers from blood or urine like miRNA. They can lead to early diagnosis, individualized therapy according to molecular profile, improved therapy response, minimized side effects of therapy, decreased incidence and recurrence rates. It is important to design new screening programmes where miRNA will play a key role.

Acknowledgments

Dr Truţa Anamaria acknowledges financial suport from an POSDRU grant no. 159/1.5/S/138776 with title:”Model colaborativ institutional pentru translatarea cercetarii biomedicale in practica clinica –TRANSCENT”. The authors thank Tudor Fat for technical assistance in graphic design.

References


Morais DR, Reis ST, Viana N, et al. The involvement of miR-100 in bladder urothelial carcinogenesis changing the expression levels of miRNA and proteins of genes related to cell proliferation, survival, apoptosis and chromosomal stability. Cancer Cell Int 2014;14(1):119.


CYP=cytochrome P, DNA=deoxyribonucleic acid, EGF=epidermal growth factor, EGFR=epidermal growth factor receptor, EMT=epithelial mesenchymal transition, EORTC=The European Organization for Research and Treatment of Cancer Scoring System, ERCC=excision repair cross complement, FISH=fluorescence in situ hybridization, FGFR=fibroblast growth factor receptor, G=guanine, G1=first growth phase of cell cycle, HAP=haemagglutin proteinase, HIF=hypoxia inducible factor, HPV=human papilomavirus, IL=interleukin, LPS=lipopolysaccharide, MDM=murine double minute, NF=nuclear factor, NRF=nuclear respiratory factor, PAQR3=progestin and adipoQ receptor family member III, PCR=polymerase chain reaction, RT=reverse transcriptase, S=synthesis phase of cell cycle, T=timine, TLR=toll like receptor, XPC/D=xeroderma pigmentosum complementation group C/D, XRCC=x ray repair cross complementing.

Abbreviations and acronyms: BCG=Bacillus Calmette Guerin, Bcl=B cell lymphoma, C=cytosine, CIS=in situ carcinoma,