



## **Review on Clinical and Molecular Diagnosis of Periampullary carcinoma**

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### **Abstract**

Cancer is one of the predominant diseases and the incidence is largely seen in men when compared to women. Periampullary carcinoma (PC) is an uncommon heterogeneous group of cancer arising from the head region of the pancreas, distal common bile duct and the duodenum. PC can be diagnosed conventionally by clinical and molecular evaluations. Here we evaluate the best way of diagnosis for periampullary carcinoma. Clinical diagnosis deals with the imaging studies including PET (Positron Emission Tomography scan), Computerized Tomography (CT scan), Endoscopic Ultrasonography (EUS), ERCP (Endoscopic Retrograde Cholangiopancreatography) and pathological examination. Molecular examination deals with the evaluation of gene mutation and protein sequences; both the evaluations have their limitation but they have specific application to detect the disease. Comparing with all the imaging and pathological techniques, EUS is the best way to detect cancer because it has the high throughput screening especially in the staging of tumors. Molecular diagnosis is very much focused in the identification of the gene responsible for the carcinoma and it can be achieved by some of the downstream processes such as PCR, RFLP and sequencing.

**Keywords:** periampullary carcinoma, clinical diagnosis, EUS, molecular diagnosis.

### **Introduction**

Cancer is a paramount public health concern over a century and it is the leading lethal disease in the world. Based on the survey conducted by the National Center for Health Statistics (NCHS), cancer holds the second

place after heart diseases (Jemal A et al., 2009). The possibility of cancer is higher in men (42%) when compare to women (38%) (Jemal A et al., 2009). The exact reason which influences cancer in men is not

well-studied but, researchers have assumed environmental changes, imbalance (or) error in endogenous hormones and nutritional intake may influence the prevalence of cancer and death in both men and women (Wiren S et al., 2014). Rebecca et al., stated that the risk of cancer is higher in women (54%) who are younger than 50 years than in men (3.4%) because of the high prevalence in breast, genital and thyroid (Rebecca et al., 2016). Cancer in the digestive system comprised of 19% of the total incidence of cancer-related diseases. Intestinal epithelial system is one of the wide investigated self-renewal lineage specification were the epithelium of Gastrointestinal (GI) tract takes about 2-7days for attaining normal conditions.

### **History of Periapillary Carcinoma:**

PC is an uncommon heterogeneous group of cancer arising from the head region of the pancreas, the distal common bile duct and the duodenum. This PC differs from ampullary carcinoma, it has topographically located in the region of the ampulla of Vater, which possesses three anatomical structures such as ampulla, the intraduodenal portion of the bile duct and the intraduodenal portion of the pancreatic duct (Yasuo Imai et al., 1997). Abraham Vater, a German Anatomist discovered Ampulla of Vater in 1720. The first pancreatic head resection was performed by Alessandro Codivilla during late 1800s A.Codivilla (1898). Halsted performed ampullectomy, one of the surgical breakthrough procedure in 1899 for the treatment of ampullary and periampullary tumours Halsted WS (1899) After Halsted contribution, a German Surgeon, Walther Kausch performed the first successful one-stage pancreaticoduodenectomy for the treatment of ampullary and PC W.Kausch(1909). Though ampullectomy is a breakthrough in surgical oncology, this procedure possess some limitations such as lesser radicality, higher rates of tumor recurrence and also lower surgical morbidity (Patel Ret al., 2012, Knox RA et al.,1986,Alstrup N et al.,1996. Asbun HJ et al., 1993). Finally, pancreaticoduodenectomy was introduced by Whipple in 1935. Whipple performed his operation 25 years after Kausch on 1934. By comparing pancreaticoduodenectomy with other practices such as ampullectomy, Whipple procedure is the most radical form of surgery. Whipple procedure is a preferable method for patients who are suffering from malignant periampullary diseases. For reducing the surgical risks associated with ampullectomy, many centres have developed the expertise treatment of pancreaticoduodenectomy for premalignant diseases,

of both ampulla of Vater and periampullary carcinoma. Pancreaticoduodenectomy clearly focuses on the high peri-operative morbidity and to ensure the quality of life of patients performing after this radical surgery (Ceppa EP et al., 2013, Grobmyer SR et al.,2008, Yoon SM et al.,2007, Rattner DW et al.,1996).

### **Prevalence and Survival Status**

Klemptnauer et al stated that the overall incidence is increasingly seen in men in which most of the patients are over the age group of 60 (Klemptnauer J et al., 1998). Klemptnauer et al projects his study through population basis and revealed that age-standardized incidence rates of 3.8 per 1000000 inhabitants in men and 2.7 per inhabitants in women (Benhamiche AM et al., 2000). Prevalence of PC exhibit 50%-70%, ampullary and head carcinomas of pancreas project 15%-25%, biliary and duodenal cancers shows in 10%.The survival status and prognostic level of patients depend upon the tumor stage and tissue of origin. PC shows high survival rate when compared with other carcinomas such as duodenal and pancreatic tumours (Sarmiento JM et al., 2001, O'Connell JB et al., 2008. Burgos L, 2008).

### **Risk factors and Symptoms**

The risk factors for pancreatic cancer and PC have been studied since 1978 were the age is one of the important risk factor in both periampullary and pancreatic carcinoma. About 80% of periampullary cases are seen between the age of 60 to 80 years. Apart from genetic risk factors, environmental exposure like active and passive smoking, alcoholism and also nitrosamines exposure may influence the risk of pancreatic cancer and periampullary cancers (Gold EB et al., 1998, Miller BA et al., 1993). The clinical manifestation of PC appears initially as a small neoplastic obstruction that is found either in the bile duct or pancreatic duct. The pathological symptoms of PC are more or less similar from patient to patient (Binmoeller KF et al., 1993). The most commonly faced symptoms of ampullary and PC are obstructive jaundice, ferroperenic anaemia and obstruction of bile flow through intra (or) extrahepatic bile ducts (Albores-Saavedra Jet al., 2009, Binmoeller KF et al., 1993). Some of the common signs and symptoms of PC are abdominal pain, weight loss, nausea, dyspepsia or vague discomfort in the upper hemiabdomen and vomiting (Holzheimer RG et al., 2001). Apart from malignant periampullary diseases, benign diseases have a variable symptomatology such as bile duct stone and acute pancreatitis.

Moreover, benign cases are complex with distant symptoms. These complex cases can be diagnosed only by the endosonographic method and not by biopsy or convention imaging Cecilia Castillo (2010).

### **Diagnosis of periampullary carcinoma:**

#### **Imaging studies:**

Imaging methods is one of the milestones in clinical diagnosis of diseases and disorders of mankind. Some of the important imaging techniques used particularly for the ampullary and PC are computed tomographic scanning (CT scan), endoscopic retrograde cholangio pancreatography (ERCP), and endoscopic ultrasonography (EUS) (Kim JH et al., 2002). ERCP and EUS imaging studies are very useful in evaluating the nature of the ampullary and PC. These techniques are commonly used in the diagnosis of carcinoma and adenomas in periampullary region. It allows in evaluating the nature of the lymph nodes in suspected patients having periampullary cancers. These imaging techniques are helpful for the surgeon in assessment of therapy. Every imaging technique possess its own specific application in which, EUS is the best technique ever for evaluating the tumor staging (Itoh A et al., 1997, Chen CH et al., 2001, Cannon ME et al., 1999, Schwarz M et al., 2001, Chen CH et al., 2001). Magnetic resonance imaging is the greatest method for the assessment of nodal staging of PC. CT and PET scanning can reveal the metastases effect of cancer which is not seen through EUS. While comparing with all imaging techniques, EUS only possess a high rate of accuracy than other imaging studies (Menzel J et al., 1999).

#### **Pathology Examination:**

##### **Macroscopic examination:**

PC usually shows a swelling in the duodenal lumen. If the bulge remains in the duodenal lumen the duodenal mucosa may lose its original form or else if the tumor is confined to the ampullary lumen. The duodenal mucosa may appear normal in another way, the tumour growth presents around the ampulla (Cubilla AL et al.,1985) Periampullary tumours can be classified pathologically as intra-ampullary, periampullary and mixed types based on the location (Lechago J et al.,1996)

#### **Microscopic Examination:**

Most of the malignant ampullary tumors are adenocarcinomas. Generally, these malignant ampullary tumors have a superficial papillary with villous adenoma (or) villoglandular polyps. Tumor groups of ampullary and PC are classified under the extra-hepatic biliary tree. This classification of carcinoma of the extrahepatic bile ducts, published in 2000 by the world health organisation (Compton CC (1997), Clark BM et al., 2000).

#### **Tissue Diagnosis:**

Histological evaluation is one of the main diagnosis of PC. This evaluation can be projected through endoscopy and biopsy. These methods plays a vital role in obtaining an accurate preoperative diagnosis. More surgical practices needs to be done for adenomas and invasive carcinomas (Treitschke F et al., 1999, Lewin KJ et al., 1992). Villous adenoma should not be diagnosed superficially or else malignant part will be missed (Fenoglio-Preiser CM et al., 1999). Treitschke et al reported that by the evaluation of frozen sections of both ampullary and PC, periampullary frozen tissues shows higher accuracy than ampullary carcinoma (Treitschke F et al., 1999).

#### **Molecular Diagnosis of periampullary carcinoma:**

##### **K-ras:**

Ki-ras (Kirsten rat sarcoma) viral oncogene is a GTPase were the K-ras codes for a specific protein which performs the normal tissue signalling pathways (McGrath JP et al., 1983, Popescu NC et al., 1985). Chromosomal location of the Ki-ras gene is 12p12.1, which is the short (p) arm of chromosome 12 at position 12.1 (Homo sapiens Annotation release 1088, GRCh38.p7). K-ras gene mutations most commonly seen in colorectal cancers located in places ascending from the colon to rectum (Yamauchi M et al., 2012, Rosty C et al.,2013). Mutational changes have been observed specifically at codon 12,13 and 61 in various human carcinoma with distant frequencies (Bos U et al., 1987,Lemoine RN et al.,1989). Incidence of Ki-ras mutation was observed in pancreatic carcinoma. Ki-ras gene mutation shows high level of incidence rate when compared to other gene mutation in PC (Smit VT et al., 1988, Almoguera C et al.,1988, Chung CH et al.,1996).

### **APC:**

Adenomatous polyposis coli (APC) gene codes for APC protein in humans (Nishiho I et al.,1991). This APC gene involves in the cell adhesion process and serves as a negative regulator which controls beta-catenin concentration and interacts with E-cadherin. Alterations in APC gene may affect the APC protein which may lead to severe outcomes like colorectal cancer and PC (Markowitz SD et al., 2009) Barth et al stated that mutation of APC gene occurs in ampullary and periampullary carcinoma next to colorectal cancer (Barth et al., 1997) Similarly, Vogelstein et al revealed that the prevalence of APC gene mutation in PC is 67%, 50% in ampullary adenomas, and 46% in non-ampullary adenomas (Vogelstein B et al.,1988). Achille et al described that the loss of heterozygosity on chromosome 5q (APC locus) may lead to APC gene silencing associated with mutation (Achille et al.,1996):

### **Beta-catenin:**

Beta-catenin is a gene that codes for the protein beta-catenin. This protein molecule plays an important role in cell adhesion and downstream process in Wnt signalling pathway by the influence of APC gene (Barth et al., 1997). Cell adhesion can be formulated by the interaction with Tcf/Lef-12 transcription factors and activation of specific genes (Behrens J et al., 1996). According to Morin et al, mutations in exon 3 of the beta-catenin gene at the sites of phosphorylation leads to the progression of variety of cancers (Morin PJ et al., 1999). Sometimes the altered product of APC gene may control the level of beta-catenin in the cytoplasm by direct binding towards the receptors of beta-catenin and regulates the NH2-terminal phosphorylation (Rubinfeld B et al., 1993, Munemitsu et al., 1995). (Asif Rashid et al., 2001) In a Chinese population-based study the prevalence of the beta-catenin gene mutation was seen with 14.3% in ampullary carcinoma whereas 9.1% was seen in PC (Asif Rashid et al., 2001). These carcinomas with missense mutation mainly affect the serine (or) threonine of GSK-3b phosphorylation important for beta-catenin degradation (Asif Rashid et al., 2001).

### **p53 Tumour suppressor Gene:**

p53 is cellular tumor antigens were it is situated in the short arm of chromosome 17. It exhibits a common substitution of an arginine for a proline at codon 72. Scarpa et al states that high mutational frequency of p53 gene can be seen in the sporadic ampullary

carcinoma (Scarpa A et al.,1993). Apart from colon cancer p53 gene mutation occurs at CPG dinucleotides (Rideout WM et al., 1990).

### **Indian scenario of periampullary carcinoma:**

Supriyo Ghatak, a Gastro surgeon who handled a rare case of 44 year old women with jaundice and also with HIV positive. Her CT scan revealed with an ill-defined periampullary tumor. She was then successfully operated by classical Whipple's pancreatoduodenectomy and also jejunostomy. Her tissue biopsy reported with 2cm well-differentiated carcinoma of the periampullary region with no perineural invasion. This case report was one of the milestones in surgical oncology (Li L et al., 2007, Wildi S et al., 2001, Guth AA et al., 1996). In Indian scenario, compare to imaging techniques molecular evaluation of PC is not well studied in the aspect of diagnosis.

### **Conclusion:**

Cancer is an incurable disease in the current medical scenario. From the statistics, 19% of cancer comes under the GI tract carcinoma. Among the GI tract cancer PC is an uncommon cancerous condition. It has the highest incidence in men when compared to women. Generally clinical diagnosis such as pathological diagnosis comprises of macroscopic and microscopic examination were the macroscopic examination is concerned with the surgical aspects whereas microscopic evaluation deals with the histological examination of the biopsy sample. When comparing with these two evaluation processes, microscopic evaluation is widely preferable method than macroscopic examination. We can identify the prevalence of accumulated protein in cytoplasmic level in the aspect of microscopic identification. Another important method is EUS which shows high accuracy of evaluation and best technique for evaluating the tumour staging. Other than clinical diagnosis, the molecular diagnosis has a distant role of evaluating cancer. Mainly it deals with the diagnosis of alternation of nucleotide and protein sequences in molecular level. Though clinical and molecular diagnosis has both advantages as well as limitations, clinical diagnosis is meant for the primary study of the carcinoma whereas molecular diagnosis is for the identification of the root cause of the carcinoma.

### **Authors' contributions**

All authors are equally contributed for writing and final approval of the manuscript.

## Conflict of interest

The authors have no conflict of interest to declare.

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**How to cite this article:**

Balasubramanian Venkatesh, Lakshmanan Anand, Vijaya kumar Padamavathi, Vellingiri Balachandar. (2016). Review on Clinical and Molecular Diagnosis of Periampullary carcinoma. *Int. J. Adv. Res. Biol. Sci.* 3(9): 210-216.

**DOI:** <http://dx.doi.org/10.22192/ijarbs.2016.03.09.028>