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# Clinical Prognosis of AKT2 and COX2 Mutation on Colorectal Cancer

**Caroline Tatim Saad[1,2], Maria Cristina Sartor[1], Camila Cavalcanti Barcelos Rodrigues[3], Alexandre Bueno Merlini[4], Mário Rodrigues Montemor Netto[2] and Jorge Eduardo Fouto Matias[1]**

[1]*Universidade Federal do Paraná (UFPR) - Curitiba, Paraná, Brazil*

[2]*Universidade Estadual de Ponta Grossa - Ponta Grossa, Paraná, Brazil*

[3]*Universidade Nove de Julho - São Bernardo do Campo, São Paulo, Brazil*

[4]*Instituto do Câncer do Estado de São Paulo - São Paulo, São Paulo, Brazil*

***Corresponding author**

Alexandre Bueno Merlini, Alameda Itanhaém, 289 - Alphaville. Santana de Parnaíba, São Paulo, Brazil

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## Introduction

Cancer has become one of the most mortal diseases in the world. It was estimated in 2018 18.1 millions new cancer cases. The colorectal cancer (CRC) is the third most common type of cancer in men and the second in women around the world [1]. The incidence risk in the occidental population is 5% to 6%, and it can increase to 15% to 30% when a first degree relative has the diagnoses. In hereditary predisposition cancer syndrome like the Lynch syndrome it can grow up to 80% [2].

Some lifestyle habits may influence the development of colorectal cancer, such as smoking, physical inactivity, overweight and obesity, red meat and processed food intake and alcohol abuse, as they lead to changes in metabolism, which in turn have cellular and molecular implications [3].

Over the last years, studies have been improving the knowledge about the hallmarks of cancer, and that also includes the next generation of hallmarks, that can be metabolic, genetics and inflammatory. This similarity between the diseases shows predictors of evolution and therapeutic responses. The physicians are always trying to put their patients in one of the hallmarks groups, but it is hard to use it in the clinical practice, because patients with similar clinical profiles have different outcomes [4]. The personalized medicine in Oncology works with ´the unique tumor principle' that connects the pathological molecular changes in tumors and the contextual environment in each patient. This has been helpful to create new strategies to combat cancer [5].

Recent studies have shown the impact of inflammation in CRC. Rudolf Virchow, in 1863, was the first to observe the relationship between cancer and inflammation [6]. The inflammatory process is a possible key to understand the role pathogenesis process of CRC, especially in the promotion. This is a changing factor in cancer staging and prognosis knowledge [7].

Carcinogenesis involves several pathways, like the traditional and the alternative. But there are other pathways also involved, like the AKT2 and COX 2 pathways.

The AKT2 is a frequent alteration in CRC. It is a survival oncoprotein that regulates multiple cellular processes like growth, metabolism, proliferation and migration. In tumor cells the abnormal expression of the AKT2 can result from some major events like the overexpression or amplification AKT, overexpression of his receptor, mutation or deletion of the suppressor gene PTEN or a negative regulator of PI3K [8, 9].

The cyclooxygenase 2 (COX 2) is knowing as one of the keys to the colon carcinogenesis, is considered involved in inflammation and progression of different types of carcinomas [10]. It is an inducible isoform of prostaglandin H synthase that mediates prostaglandin synthesis during inflammation, an immediate-early response gene normally absent from most cells [11, 12].

This article analyses the correlation between CRC and the inflammatory hallmarks AKT2 and COX 2.

## Methodology

The study used a clinical and pathology database of 211 patients with advanced colorectal tumors from a private clinic in Ponta Grossa - Paraná - Brazil, who were submitted to surgery for the treatment of colorectal cancer from 2010 to 2015. It was approved by the Ethical Review Board from Federal University of Paraná, protocol 2.504.578, approved in 2018, February 21th.

Written and informed consent was obtained from each patient included in the study. Its protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

## Inclusion Criteria

Cases of CRC diagnoses between 2010 to 2015 of the Ponta Grossa Medical Pathology laboratory database.

## Exclusion Criteria

Patients without or with incomplete medical records or familial adenomatous polyposis cases.

It was collected information from the medical records about age, sex, comorbidities, primary tumor location, which were subdivided into three groups: proximal colon (right colon to transverse colon tumors), distal colon (from splenic flexure to sigmoid colon) and rectal tumors, postoperative course, anatomopathological classification, degree of cell differentiation and tumor staging by pTNM classification [8]. Cases were classified according to histological type in adenocarcinoma, mucinous adenocarcinoma, villous adenocarcinoma, squamous cell carcinoma.

The surgical blocks were, right after resection, fixed in formalin. The histological technique was then performed, including the steps of gradual dehydration, diaphanization, infiltration and paraffin embedding of the samples. Through each paraffin block, histological sections were then stained by hematoxylin-eosin (HE) technique. Subsequently, they were submitted to the array arrangement of tissue mycroarray (TMA). The TMA consists of making multi-sample blocks in order to gather several samples in a single paraffin block [9, 10].

After the TMA preparation, they were prepared for immunohistochemistry for the following antibodies rabbit anti-COX-2 polyclonal antibody (Spring Bioscience, Pleasanton, CA, USA).

The slides were analyzed for marker expression, and then the markers expression, tumor staging and patient outcomes were analyzed to identify relationships between the markers and disease prognosis.

## Statistics Analyses

The comparison of two groups in relation to quantitative variables was performed using Student's t-test for independent samples. The association between markers was evaluated by estimating the Pearson correlation coefficient. The normality condition of the variables was assessed by the Kolmogorov-Smirnov test. For the determination of cutoff points for the markers, associated with metastasis, degree of differentiation and topography, ROC curves were adjusted and the areas below the curves (AUC) were evaluated. The survival time of patients after surgery was described by a Kaplan-Meier curve and the analysis of the association of variables with survival was performed by adjusting Cox regression models. The Wald test was used to evaluate the variables. Values of $p < 0.05$ indicated statistical significance. Data were analyzed using the computer program Stata / SE v.14.1. StataCorpLP, USA.

## Results

A total of 211 patients were analyzed with median age 63,4 (±13,0), 110 (52,1%) female, 101 (49,1%) male. 72 (63,2%) were declared smokers, 32 (30,8%) were declared alcoholics, 97 and 107 patients had no information on their medical reports respectively . 136 (66,7%) of the tumor was localized in the left colon, 48 (23,5%) were in the right colon and 20 (9,8%) in the rectal. Two cases had tumor in both sides (C/S e CT/AD). 78, 8% of the patients had partial colectomy. The hallmarks presence is shown in Table 1.

**Table 1: Hallmarks present in the blocks.**

| Hallmarks | n | Average | Median | Minimum | Maximum | Standard deviation |
|---|---|---|---|---|---|---|
| AKT2 SUP | 199 | 21,0 | 19,8 | 0,6 | 60,3 | 14,8 |
| AKT2 PROF | 192 | 21,3 | 19,8 | 0,4 | 59,2 | 14,5 |
| COX2 sup | 200 | 18,2 | 17,1 | 0,2 | 55,0 | 11,9 |
| COX2 prof | 176 | 18,2 | 15,2 | 0,2 | 52,9 | 11,9 |

About the metastasis, 34 (17, 9%) of the patients had metastasis at diagnoses and 60 (31, 9%) had at some point of the disease.

The table 2 shows the relation between metastasis and the hallmarks presents in the samples.

**Table 2: Metastasis in the Hallmarks Presence.**

| Hallmarks | Metastasis at dx | n | Metastasis | n |
|---|---|---|---|---|
| AKT2 SUP | No | 146 | No | 120 |
| | Yes | 32 | Yes | 57 |
| AKT2 PROF | No | 142 | No | 118 |
| | Yes | 32 | Yes | 54 |
| COX2 sup | No | 148 | No | 122 |
| | Yes | 31 | Yes | 56 |
| COX2 prof | No | 129 | No | 107 |
| | Yes | 30 | Yes | 50 |

For the marker COX2 sup was found a significant difference in the topographies, on the comparison to right and left. Table 3 shows the localization of the tumor in each hallmarker.

**Table 3: Tumor Localization by Hallmark.**

| Hallmark | Topography | n | Average | Median | Minimum | Maximum | Standard deviation | Deviation p value |
|---|---|---|---|---|---|---|---|---|
| AKT2 SUP | Right | 46 | 25,5 | 24,6 | 1,38 | 58,9 | 16,2 | |
| | Left | 127 | 19,8 | 18,9 | 0,58 | 60,3 | 14,3 | |
| | Rectal | 20 | 20,2 | 20,9 | 0,64 | 41,7 | 12,0 | 0,073 |
| AKT2 PROF | Right | 43 | 24,0 | 21,2 | 2,73 | 54,9 | 14,8 | |
| | Left | 127 | 20,8 | 18,5 | 0,42 | 59,2 | 14,7 | |
| | Rectal | 16 | 19,7 | 19,9 | 0,40 | 47,8 | 13,1 | 0,409 |
| COX2 sup | Right | 47 | 22,1 | 19,9 | 0,23 | 55,0 | 14,0 | |
| | Left | 128 | 17,1 | 16,0 | 0,68 | 44,9 | 11,0 | |
| | Rectal | 19 | 16,5 | 13,7 | 2,53 | 33,4 | 9,8 | 0,040 |
| COX2 prof | Right | 38 | 21,4 | 21,4 | 1,94 | 52,9 | 12,9 | |
| | Left | 120 | 17,5 | 14,9 | 0,29 | 52,4 | 11,5 | |
| | Rectal | 11 | 16,4 | 14,6 | 3,92 | 37,3 | 10,5 | 0,183 |

## The patient survival is shown in Table 4.

**Table 4: Patient survival in months.**

| Death | n | % | Follow up time (months) | |
|---|---|---|---|---|
| | | | Mean (standard deviation) | Median (minimum - maximum) |
| No | 137 | 69,2 | 37,8 (21,7) | 36,1 (0,13 – 80,9) |
| Yes | 61 | 30,8 | 15,8 (15,7) | 13,8 (0,03 – 60,1) |
| Total* | 198 | 100,0 | 31,1 (22,5) | 28,1 (0,03 – 80,9) |

Patients survival depends of a lot of variables, in table 5 is shown the correlation between the variables age, sex, live habits, tumor characteristics and hallmarks. The statistics analyses show that the T and N stages, the presence of metastasis in the diagnoses or after, compromised margin and the patol stage have relevance in patient survival. The presence of the AKT2 prof in the sample is correlated to decrease the survival time.

**Table 5:**

| Variables | n | % death or media no death / death | P value * | HR | IC 95% |
|---|---|---|---|---|---|
| Age (years) | 190 | 62,1 / 64,8 | 0,158 | 1,01 | 0,99 - 1,04 |
| Sex | | | | | |
| Female (ref) | 105 | 28,6% | | | |
| Male | 93 | 33,3% | 0,396 | 1,24 | 0,75 - 2,05 |
| Smokinh | | | | | |
| No (ref) | 42 | 23,8% | | | |
| Yes | 72 | 26,4% | 0,933 | 1,03 | 0,48 - 2,22 |
| Alcholism | | | | | |
| No (ref) | 72 | 26,4% | | | |
| Yes | 32 | 21,9% | 0,500 | 0,74 | 0,31 - 1,77 |
| Histology | | | | | |
| Mucinoso (ref) | 23 | 21,7% | | | |
| Tubular | 165 | 32,1% | 0,249 | 1,72 | 0,69 - 4,30 |
| Outhers | 8 | 25,0% | 0,461 | 1,86 | 0,36 - 9,64 |
| T staging | | | | | |
| T1 ou T2 (ref) | 17 | 5,9% | | | |
| T3 | 100 | 27,0% | 0,095 | 5,49 | 0,75 - 40,4 |
| T4 | 63 | 41,3% | 0,021 | 10,6 | 1,43 - 77,9 |
| N staging | | | | | |
| N0 (ref) | 60 | 23,3% | | | |
| N1 | 66 | 24,2% | 0,821 | 1,09 | 0,53 - 2,23 |
| N2 | 52 | 46,1% | 0,004 | 2,67 | 1,37 - 5,20 |
| Metastatic Lymph Nodes | 186 | 3,5 / 4,1 | 0,089 | 1,03 | 1,00 - 1,07 |
| Total lymph nodes | 187 | 25,1 / 19,7 | 0,088 | 0,98 | 0,96 - 1,00 |
| Tumor size | 196 | 56,4 / 58,4 | 0,590 | 1,00 | 0,99 - 1,01 |
| Metastasis in dx | | | | | |
| No (ref) | 156 | 24,4% | | | |
| Yes | 34 | 58,8% | <0,001 | 3,81 | 2,19 - 6,61 |
| Metastasis | | | | | |
| No (ref) | 128 | 18,0% | | | |
| Yes | 60 | 60,0% | <0,001 | 4,60 | 2,71 - 7,80 |
| Compromised Margin | | | | | |
| No (ref) | 125 | 26,4% | | | |
| Yes | 61 | 41,0% | 0,014 | 1,93 | 1,14 - 3,26 |
| Neoadjuvante | | | | | |
| Yes (ref) | 25 | 28,0% | | | |
| No (ref) | 166 | 30,7% | 0,530 | 1,29 | 0,58 – 2,84 |
| Adjuvante | | | | | |
| Yes (ref) | 132 | 26,5% | | | |

| | | | | | |
|---|---|---|---|---|---|
| No | 58 | 37,9% | 0,004 | 2,19 | 1,28 –3,74 |
| Patol stage | | | | | |
| I ou II (ref) | 40 | 12,5% | | | |
| III | 68 | 19,1% | 0,429 | 1,52 | 0,54 - 4,25 |
| IV | 26 | 50,0% | 0,001 | 6,15 | 2,17 - 17,4 |
| AKT2 superf | 186 | 20,4 / 21,7 | 0,493 | 1,01 | 0,99 - 1,02 |
| AKT2 prof | 182 | 20,2 / 24,5 | 0,049 | 1,02 | 1,00 - 1,03 |
| COX2 superf | 187 | 18,1 / 18,6 | 0,642 | 1,01 | 0,98 - 1,03 |
| COX2 prof | 166 | 17,9 / 19,1 | 0,331 | 1,01 | 0,99 - 1,04 |

The same sample can bring more than one hallmark alterations, the correlation between the hallmarks is shown on table 6. In the ones that has p<0, 05 classify as excellent | r | > 0, 90; good | r | de 0, 75 a 0, 90; moderate| r | de 0, 50 a 0, 74 and weak | r | <0, 50.

**Table 6. Hallmarks correlations.**

| Variables | n | r(X/Y) | p |
|---|---|---|---|
| AKT2 SUP x AKT2 PROF | 102 | 0,75 | <0,001 |
| AKT2 SUP x COX2 sup | 102 | 0,27 | 0,006 |
| AKT2 SUP x COX2 prof | 102 | 0,31 | 0,002 |
| AKT2 PROF x COX2 sup | 102 | 0,18 | 0,066 |
| AKT2 PROF x COX2 prof | 102 | 0,40 | <0,001 |
| COX2 sup x COX2 prof | 104 | 0,65 | <0,001 |

## Discussion

Virchow in 1863 suggested the correlation between cancer and inflammation, he had the idea that "lymphoreticular infiltrate" reflected the origin of cancer at sites of chronic inflammation. The studies made in the last years support that hypotheses and helped to understood better this relation [6, 7].

Experimental models and epidemiologic study has shown that COX 2 and AKT2 has an important role in the tumorigenesis and tumor development [8-16]. Most of them explained the COX 2 or AKT 2 using inhibition techniques. Reddy, et al. (1993) used aspirin to inhibit the colon carcinogenesis in rats, they were successful in their study but could not explain the mechanisms involved in the protect effect that aspirin had in CRC [17]. Chan, et al. (2009) studies showed that the use of aspirin after a diagnosis of nonmetastatic CRC were associated with a decreased risk of colorectal cancer–specific mortality, been stronger in the participants who had primary tumors overexpressing COX-2 [18].

Ericson (2010) made a genetic inactivation ok AKT2, in challenging microenvironments the inhibition drastically affected growth of the cells, retarding then. Their study also specify that signaling pathways in CRC can´t be trustworthy inferred using studies of other organisms or cell types [19].

The COX 2, also known as prostaglandin-endoperoxide synthase 2 (PTGS2), it's a COX isoform that is not normally expressed by the intestine cells. It's a rate-limiting enzyme that operates in the metabolic conversion of arachidonic acid to prostaglandins, it works producing prostaglandin in the inflammatory and carcinogenesis. Is believed that COX 2 has an important role in inhibition of apoptosis, immune surveillance, promotion of angiogenesis, elevation of cancer invasiveness the modulation of cell differentiation and metastasis [20, 21].

There are plenty of studies that correlate CRC and COX 2 hallmarks, but then study the early stages of the cancer, not having much information about the action of these genes in advanced cancers. Harris (2008) shows the important role that COX2 has in the carcinogenesis in breast, lung, prostate and colon cancers, concluding that the inhibition of COX2 reduces the risk of developing this 4 types of cancer.

The evidence for that is attached to the carcinogenesis that normally evolves as a progressive series of highly specific cellular and molecular changes in response to induction of constitutive over-expression of COX-2 [22]. Stamatakis, et al. (2015) said that COX2 overexpression causes a more aggressive tumor phenotype in colon carcinoma cells, being extremely important in the first stages [23].

AKT2 is a survival oncoprotein that promotes cell survival, cell cycle progression, angiogenesis, telomerase activation, and tumor cell invasiveness. AKT is one of the main mediators of survival signals, it protects the cells from undergoing apoptosis and because of that is a potentially important therapeutic target. A lot of studies were made about the activation of AKT 2 and different tumors [24].

Yuan, et al. (2000) conducted research about AKT2 and ovary

cancers. They find out that the majority of tumors with activated AKT2 were high grade and late stage, that AKT 2 has an important role in development of human ovarian cancer, especially in tumor progression and that direct inhibition of PI 3-kinase / Akt pathway induces apoptosis in ovarian cancer cells lines with PI3-kinase / AKT2 [25].

The correlation between AKT2 and CRC has also been described in the literature. Ding, et al (2014) brought results that indicate that knockdown of AKT2 reduced proliferation and enhanced apoptosis, the downregulation of Akt2 enhanced the chemo sensitivity to paclitaxel being a potential gene-targeting approach to treat CRC [26].

The results show that in the advanced CRC the presence of the mutations in AKT2 and COX 2 do not play a very important role in mortality, but the presence of AKT2 hallmark deep in the tumor is related to lower survival. Unlike other studies that show a significant action of the AKT2 in the metastasis, our results exhibit that in the long term it loses the importance.

Rychahou (2006) brings the correlation between the AKT 2 and metastasis, but there is not much knowloge of the biological way, that's because the studies have a major disadvantage of the experimental metastasis models that can be studied only in late stages of metastasis formation [9]. Agarwal (2017) proposed a model to explain the metastasis process done by Akt2, this gene inhibits the robustly upregulates MTSS1 at the mRNA and protein levels, this leads to inhibition of Src, that has multiples substrates that can affect cell proliferation, survival, adhesion and migration, preventing metastasis [8].

In conclusion we found that in advanced CRC the presence of AKT2 deeply on the tumor brings a worse diagnosis. In long term the correlation between the mutations is lost as well as their harmful action decreases in significance.

As this is a retrospective study, we faced some incomplete medical records and it was not possible to collect all information for all of the patients.

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