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Turkish Medical Student Journal publishes researches, interesting case reports and reviews regarding all fields of medicine. The primary aim of the journal is to publish original articles with high scientific and ethical quality and serve as a good example of medical publications for those who plan to build a career in medicine. Turkish Medical Student Journal believes that quality of publication will contribute to the progress of medical sciences as well as encourage medical students to think critically and share their hypotheses and research results internationally.

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- References

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Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992.p.1561-5.

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EDITORIAL

Dear readers,

I would like to start by saying thank you to Ezgi isil ERDOĐAN, our one and only English editor who is with us since the establishment of TMSJ. She has always carried the task of perfecting the journal by making miraculous last-minute touches in the process of publishing. I wish Ezgi to be successful in her career in medicine and in editorship. I am very pleased to announce that Aslıhan AKŐAR will be among our editorial board as English editor of October '17.

Balkan Medical Journal, the precious journal of Trakya University Faculty of Medicine, is among the top 100 journals in the world indexed by SCI-Expanded. We congratulate all Balkan Medical Journal editors who are our valuable academic advisors. They have always been with us and guided us since the day TMSJ was founded. As TMSJ, we will continue to exemplify them in the academic world they have introduced us to.

If we come to this issue of TMSJ; these valuable articles will contribute to the world of science. But I want to talk about the article that excites me the most: The study of flavonoids that are frequently studied in the scientific world, has been presented to our valuable readers in this issue as a cell culture study for the first time in TMSJ.

Dear readers, stay with science until October issue.

Aslı Nur ZKAN
Editor-in-Chief



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EVALUATING COMBINED EFFECT OF NARINGIN AND SALICYLIC ACID ON COLON CANCER CELL CULTURE

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ABSTRACT

Aims: Colorectal cancer is the 3rd most common cancer in the world. It affects more than a million people and causes the death of half million people annually. Flavonoids are natural products belonging to plantae and some fungal organisms that recently have started to be popular for cancer research for its strong antioxidant, anticarcinogen and anti-tumor properties. Naringin is a special chemical compound of flavonoid groups in grapefruit and useful for its antioxidant and immunostimulatory properties. Salicylic acid is a stress-specific hormone that also has an anti-tumor effects on colorectal cancer. In this study, it is aimed to evaluate the effect of naringin, salicylic acid and their combination on colon cancer cells via gene expression profiles of apoptosis genes and anti-proliferative properties.

Methods: HT29 colon cell culture was incubated in 37 C° and 5% CO₂. Salicylic acid, naringin and their combinations were applied seperately on 80% confluent cells in 11 different doses starting with 800 µM and going half of the previous. MTT survival test was performed at 24th and 48th hours after application. To see the effect on apoptosis and antioxidant pathway; apoptotic protease activating factor, B-cell lymphoma 2, B-cell lymphoma 2 associated X, B-cell lymphoma 2 - XL, Cytochrome C, Cellular inhibitor of apoptosis protein 1, Cellular inhibitor of apoptosis protein 2, Glyceraldehyde-3-phosphate dehydrogenas, Caspase 3, Livin, Survivin, p21, p27, p53 and X-linked inhibitor of apoptosis, Catalase, Glutathione peroxidase, Superoxide dismutase 1 and Superoxide dismutase 2 gene expressions were assayed on 24th and 48th hours by using real time PCR.

Results: Single and combined application of naringin and salicylic acid decreased cell proliferation at both 24th and 48th hours. Results in 48th hours were more obvious. None of the applications caused an increase in number of cells in any applied dose. In the real time PCR analysis, the expressions of apoptosis inhibitor genes that play a crucial role in antioxidant pathway were increased. The increase was more distinct in the combination of naringin and salicylic acid.

Conclusion: In this study, it is found that both salicylic acid and naringin cause a decrease in the number of colon cell culture. As for their combination it also worked well. The increase in apoptotic gene expression was exclusive. It can be said that naringin, salicylic acid and especially their combination can be a promising treatment as a supported option for colon cancer patients in the future.

Keywords: Colon cancer, salicylic acid, cell culture

INTRODUCTION

In 2013, colorectal cancer was the 3rd most common cancer and 4th leading cause of death by cancer in the world (1). It affects more than a million people and causes the death of half million people annually (2). In Europe, there are 250000 cases diagnosed annually and five-year relative survival rate is about 65 percent, however it may vary based on the state of the cancer (2).

Therefore, some precautions should be taken in order to reduce the risk of colorectal cancer such as dietary modifications because it is suggested in many articles that dietary compounds may have a role in reducing the rate of colorectal cancer and additionally digestive tract is in direct interaction with dietary components (1, 3).

Flavonoids are compounds which have beneficial health properties such as anti-oxidant, anti-viral, anti-al-

lergic, anti-inflammatory and antitumor activities by scavenging the free radicals. They are excessively found in vegetables and fruits such as citrus fruits (3, 4). Furthermore, some earlier animal model based experiments showed that fruits and vegetables have protective effects against colon cancer (4). Citrus fruits have abundant chemopreventive bioactive compounds such as flavonoids (4). Naringin is a citrus flavonoid found in grapefruit, lemon, orange and it is useful due to its anti-tumor, anti-inflammatory, anti-oxidant and anti-hypercholesterolemic activities (5).

Not only naringin is associated with reducing the risk of developing colon cancer, but also salicylic acid is found out to be effective in diminishing the risk of colon cancer (6). It has been suggested that salicylic acid plays a role in decreasing the synthesis of pro-inflammatory and potential neo-plastic prostaglandins, also increases the apoptosis (6).

As a conclusion, it is suggested that naringin and salicylic acid both have anti-carcinogenic effects in colon cancer. However, the effect of combination of naringin and salicylic acid is not investigated. In addition, the mechanisms behind such as gene expressions are not completely found out either. Therefore, the aim of this study is to evaluate the effect of naringin, salicylic acid and their combination on the number of colon cancer cells and examine gene expressions belonging to apoptosis pathway.

MATERIAL AND METHODS

Cell cultures and reagents

A cell line of colorectal adenocarcinoma HT-29 (ATCC[®] HTB-38[™]) were purchased from the American Type Culture Collection (ATCC, Rockville, Maryland, USA). The cell culture materials HAMS F 12, Dulbecco's modified Eagle's medium (DMEM) and L-glutamine, foetal bovine serum (FBS) were supplied by Gibco (Thermo, USA). PBS, trypsin EDTA, dimethyl sulfoxide (DMSO), yellow 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA). The PureLink[®] RNA Mini Kit and High Capacity cDNA Reverse Transcription Kit were supplied from Life Technologies (USA). Ethanol, ultrapure water (LiChrosolv[®] Reag) were purchased from Merck-Millipore (Darmstadt, Germany).

HT29 colon cell culture (ATCC[®] HTB-38[™]) was incubated in 37 °C in a CO₂ incubator with a humidified atmosphere of 5% CO₂. When the cells grow enough salicylic acid, naringin and their combinations were applied on them in 11 different doses starting with 800 μM and going half of the previous. In 24th and 48th hours, cell viability was measured.

Cell viability (MTT assay) and treatments

In this study, the cell viability was measured by MTT assay. In this method, HT29 cells were sown in a 96-well sterile microplate at a density of approximately 5000-7500 cells/well in 180 μl of medium 12 h before treatment. The plates were incubated in a 5% CO₂ incubator at 37 °C for 12 h for the cells to attach well. After incubation, the cells were treated with 20 μl of naringin, salicylic acid and their combinations prepared at eleven concentration levels between 1.6 - 800 μg ml⁻¹. After 24 and 48 h incubation MTT solutions (20 μl/200 μl per well of a 5 mg/ml solution) were pipetted in each well and the plates were incubated for 4 h at 37 °C. The blue formazan crystals were dissolved in DMSO (200 μl/well) and the absorbance was measured at 490 nm with a Thermo Multiscan Go Microplate Reader Spectrophotometer (Thermo Scientific, USA). The measurement of absorbance for each concentration of naringin, salicylic acid and their combinations were compared with the control.

Quantitative real-time PCR (qRT-PCR) analysis

Expression levels of the mitochondrial apoptosis genes: apoptotic protease activating factor 1 (*APAF 1*), B-cell lymphoma 2 (*BCL 2*), BCL2 associated X (*BAX*), BCL- XL, Cytochrome C (*CYC C*), cellular inhibitor of apoptosis protein 1 (*c-IAP 1*), cellular inhibitor of apoptosis protein 2 (*c-IAP 2*), Glyceraldehyde-3-Phosphate Dehydrogenas (*GAPDH*), Caspase 3 (*CASP3*), Livin, Survivin, p21, p27, p53 and X-Linked Inhibitor of Apoptosis (*XIAP*); and antioxidant genes: catalase (*CAT*), Glutathione Peroxidase (*GPX*), Superoxide Dismutase 1 (*SOD1*) and Superoxide Dismutase 2 (*SOD 2*), HT29 cells of control and 100 and 200 μM of naringin, salicylic acid and their combinations for 24 and 48 hours were analysed by qRT-PCR using the SYBR[®] Select Master Mix (Life Technologies, USA) on an ABI 7500 Real-Time PCR system with the primer pairs and PCR condition (Table 1). Gene expressions were determined as the relative fold change compared to the control and normalized with *GADPH* mRNA expressions. The comparative cycle threshold (2- $\Delta\Delta C_t$) method (User Bulletin 2, Applied Biosystems, CA) was performed to analyze the expression levels of mRNAs.

Table 1: Primer pairs of genes (7)

GENE	PRIMERS
APAF-1	F: 5'-GATATGGAATGTCTTCAGATGGCC-3' R: 5'-GGTCTGTGAGGACTCCCCA-3'
BCL 2	F: 5'-ATGTGTGTGGAGAGCGTCAA-3' R: 5'-ACAGTTCACAAAGGCATCC-3'
BAX	F: 5'-TTCATCCAGGATCGAGCAGA-3' R: 5'-GCAAAGTAGAAGGCAACG-3'
BCL XL	F: 5'-GTAAACTGGGGTCGCATTGT-3' R: 5'-TGGATCCAAGGCTCTAGGTG-3'
CYC C	F: 5'-AGTGGCTAGAGTGGTCATTCATTTAC-3' R: 5'-TCATGATCTGAATTCTGGTGTATGAG-3'
c-IAP 1	F: 5'-GCATTTTCCCAACTGTCCAT-3' R: 5'-ATTCGAGCTGCATGTGTCTG-3'
c-IAP 2	F: 5'-GCATTTTCCCAACTGTCCAT-3' R: 5'-ATTTTCCACCACAGGCAAAG-3'
GAPDH	F: 5'-AATTCCGATCTTCGACATGG-3' R: 5'-GAAAAAGCGGCAGTCGTAAT-3'
CASP 3	F: 5'-GGTATTGAGACAGACAGTGG-3' R: 5'-CATGGGATCTGTTTCTTTGC-3'
Survivin	F: 5'-TGGCCTCCTTCTATGACTGG-3' R: 5'-ACCTCACCTTGTCCCTGATGG-3'
Survivin	F: 5'-GACGACCCCATAGAGGAACA-3' R: 5'-GACAGAAAGGAAAGCGCAAC-3'
p21	F: 5'-GGCGTTTGGAGTGGTAGAAA-3' R: 5'-GACTCTCAGGGTCGAAAACG-3'
p27	F: 5'-CCGGCTAACTCTGAGGACAC-3' R: 5'-TGGATCCAAGGCTCTAGGTG-3'
p53	F: 5'-CACGAGCGCTGCTCAGATAGC-3' R: 5'-ACAGGCACAAACACGCACAAA-3'
XIAP	F: 5'-GGGGTTCAGTTTCAAGGAC-3' R: 5'-TGCAACCAGAACCTCAAGTG-3'
CAT	F: 5'-TACGAGCAGGCCAAGAAGTT-3' R: 5'-ACCTTGTACGGGCAGTTCAC-3'
GPX	F: 5'-TGGGACCAGCAAGTAAAACC-3' R: 5'-TCGCGAATGTAGAACTCGTG-3'
SOD 1	F: 5'-GTTTCGGTGACAACACCAATG-3' R: 5'-GGAGTCGGTGTGTTGACCT-3'
SOD 2	F: 5'-TCTGAAGAAGGCCATCGAGT-3' R: 5'-GCAGATAGTAGGCGTGCTCC-3'

RESULTS

Due to MTT analysis, the doses of 100 ml and 200 ml were chosen to be applied to tumor cells. Naringin, salicylic acid and their mixture had decreased the number of cancer cells on both 24th and 48th hours. Results in 48th hours were better. None of those caused an increase in number of cells in any applied dose.

In order to investigate the effects of naringin, salicylic acid and their mixture on antioxidants and apoptosis pathway, 100 and 200 μM of the molecules were studied in the real time PCR analysis. All of the results of gene expressions can be seen in Figure 1 and 2.

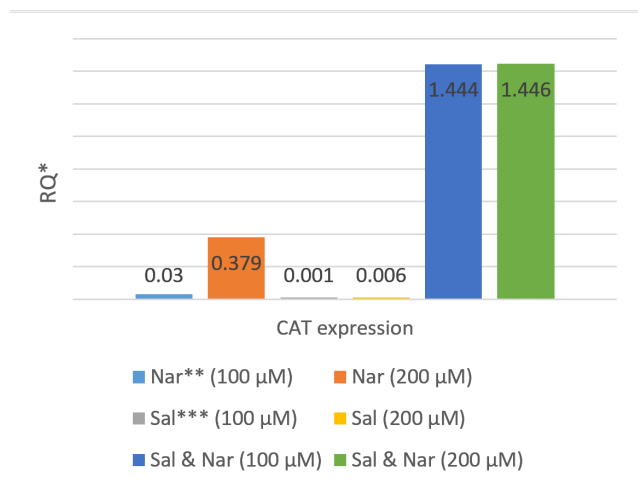


Figure 1.1: CAT expression

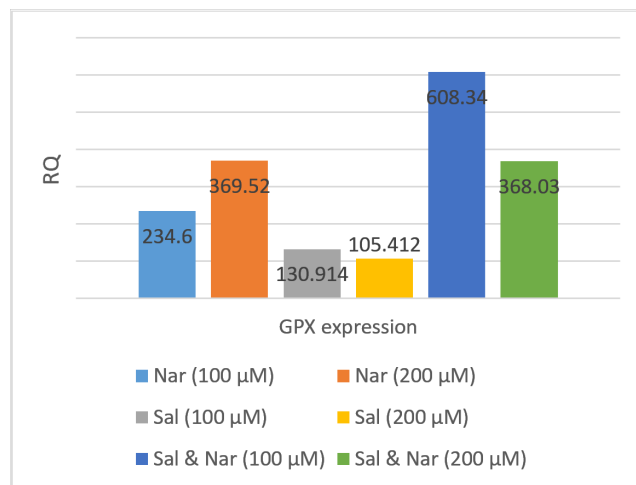


Figure 1.2: GPX expression

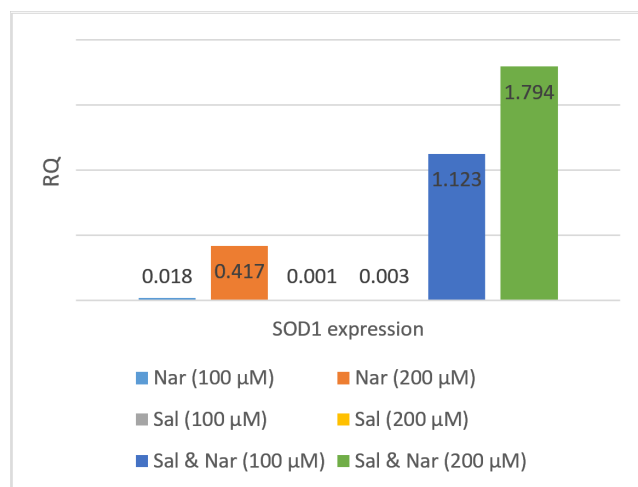


Figure 1.3: SOD1 expression

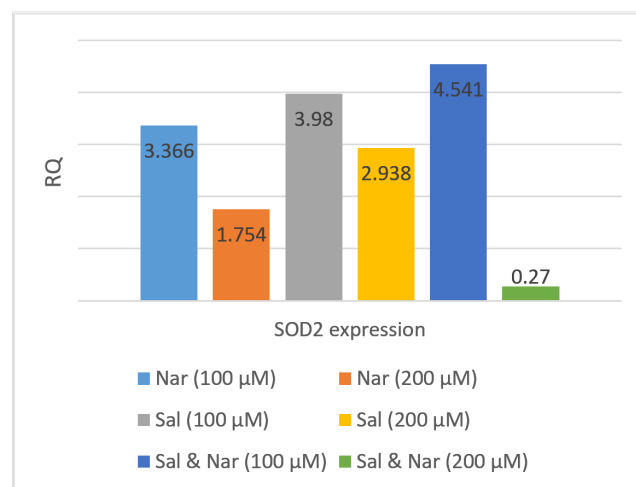


Figure 1.4: SOD2 expression

Figure 1: Expression levels of the mitochondrial apoptosis genes

(*Relative quantity unit)

(**Naringin)

(***Salicylic acid)

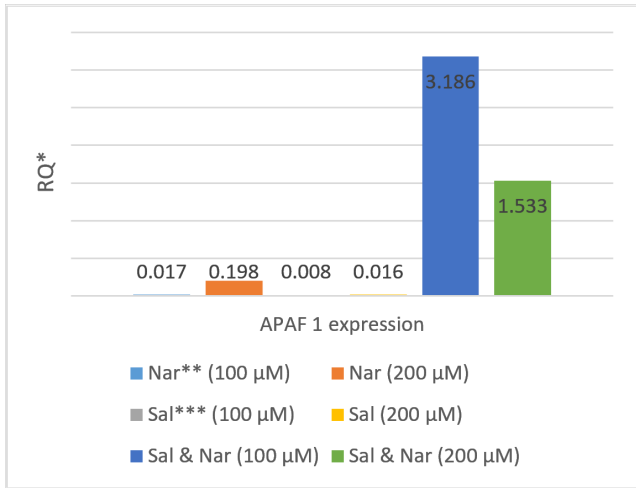


Figure 2.1: APAF 1 expression

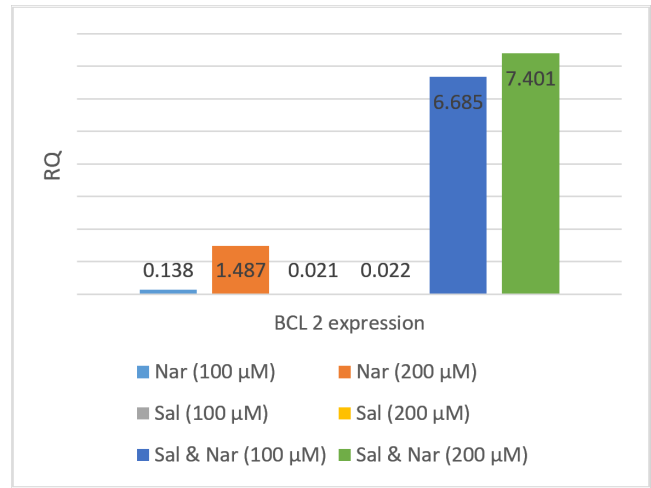


Figure 2.2: BCL2 expression

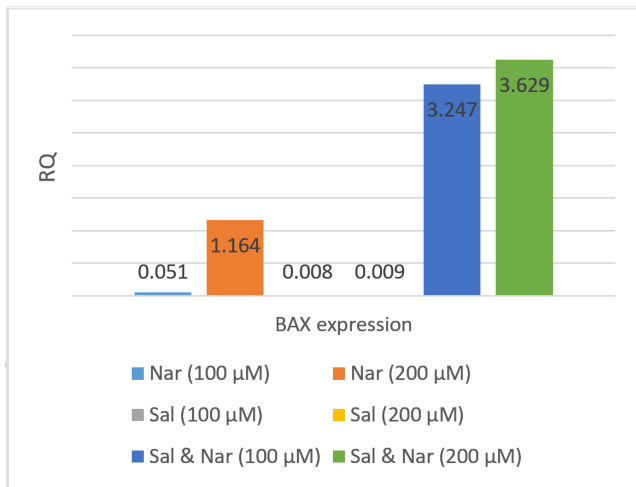


Figure 2.3: BAX expression

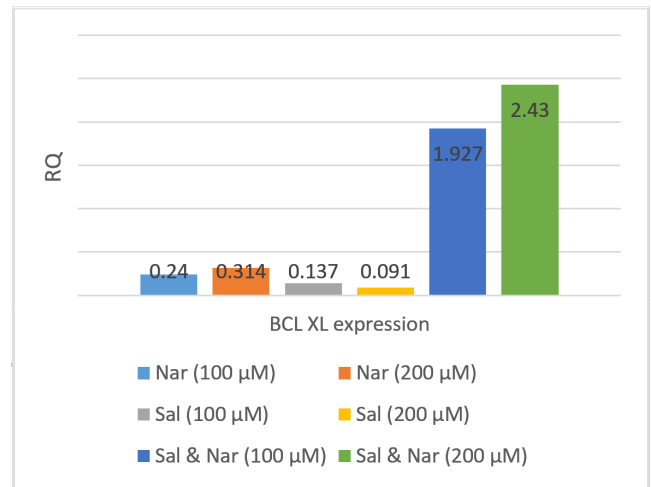


Figure 2.4: BCL XL expression

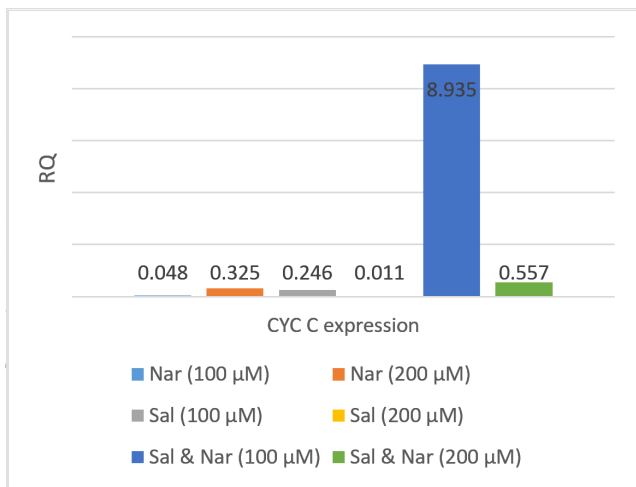


Figure 2.5: CYC C expression

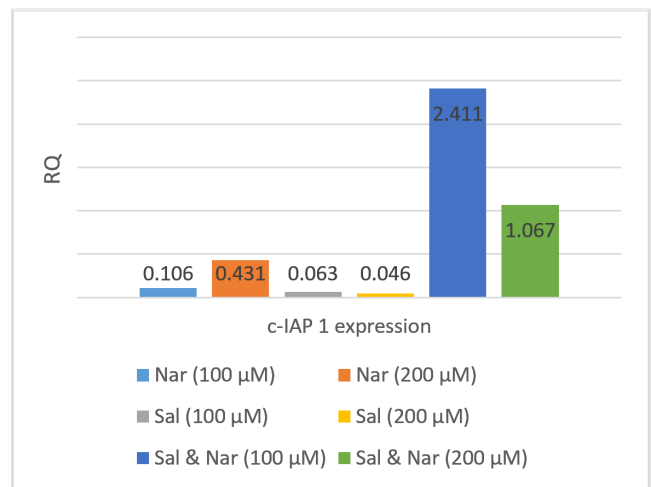


Figure 2.6: c- IAP1 expression

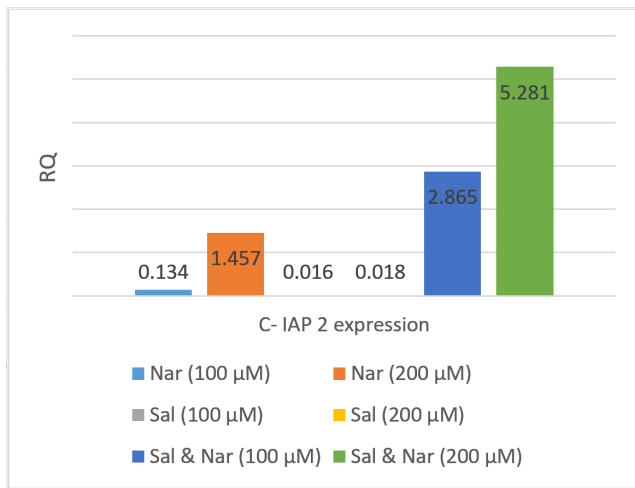


Figure 2.7: c- IAP 2 expression

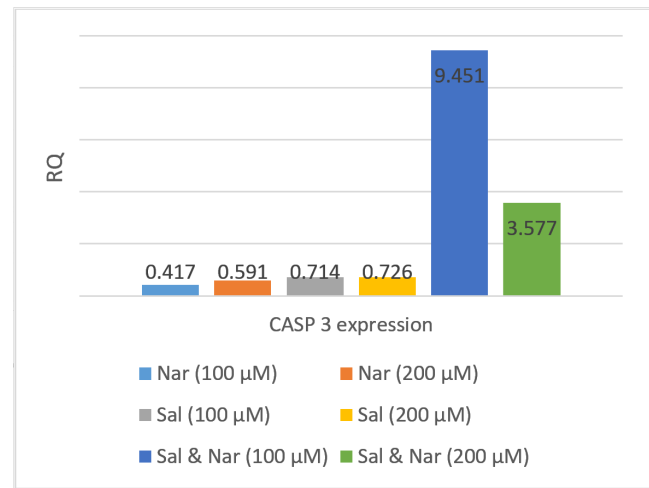


Figure 2.8: CASP 3 expression

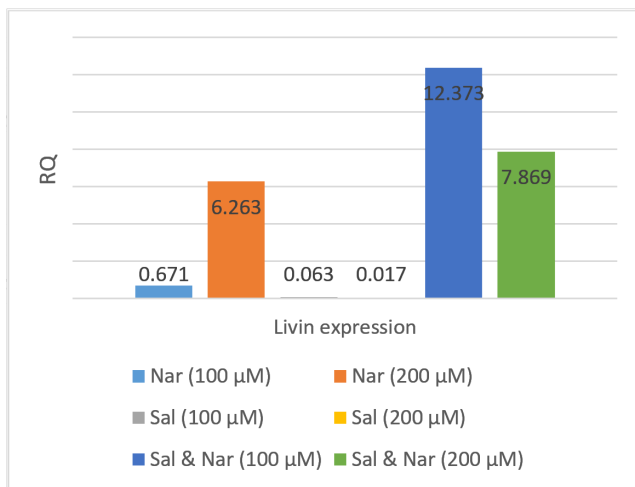


Figure 2.9: Livin expression

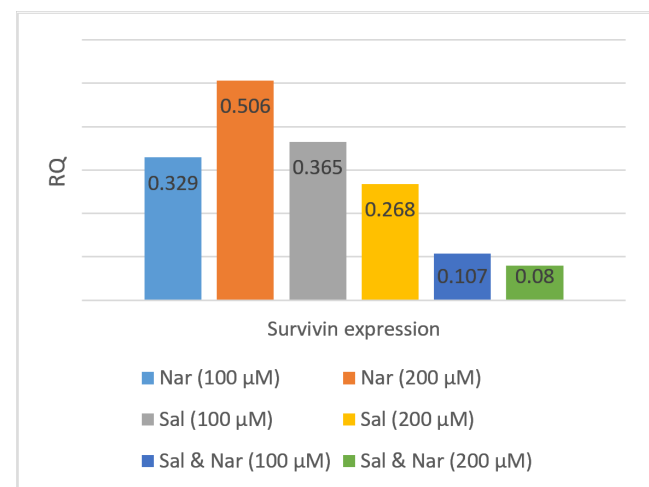


Figure 2.10: Survivin expression

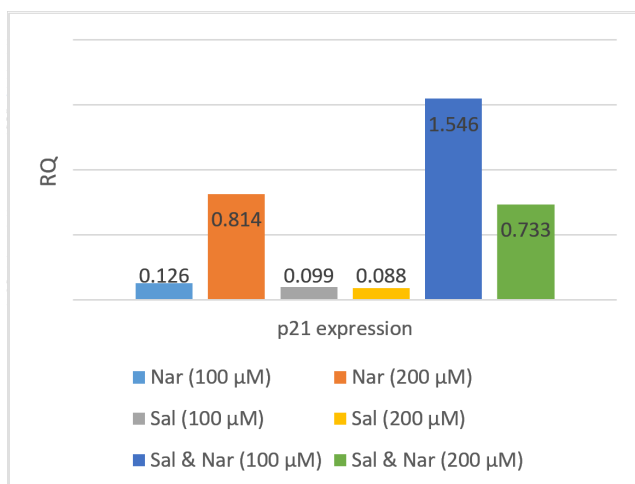


Figure 2.11: p21 expression

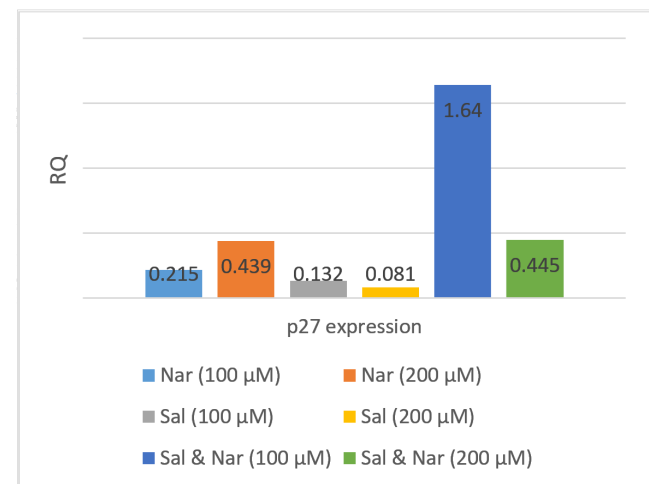


Figure 2.12: p27 expression

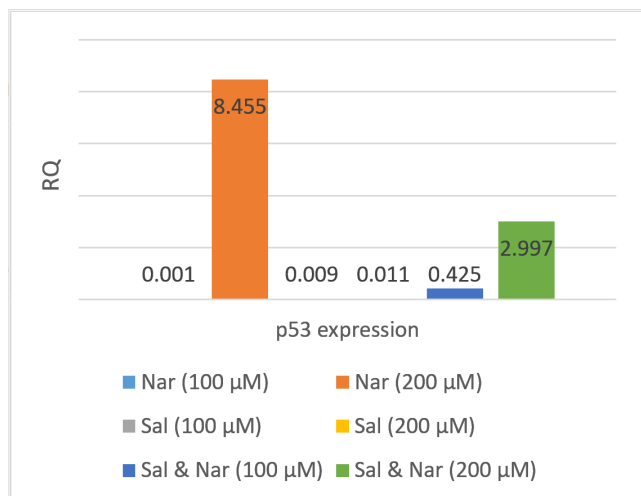


Figure 2.13: p53 expression

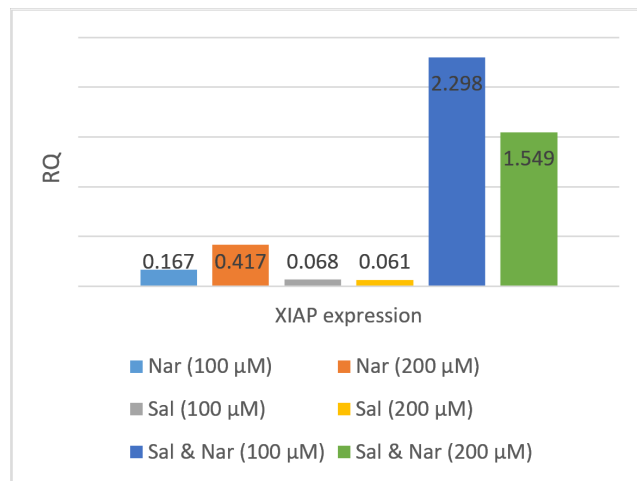


Figure 2.14: XIAP expression

Figure 2: Expression levels of the mitochondrial apoptosis genes

(*Relative quantity unit)

(**Naringin)

(***Salicylic acid)

DISCUSSION

It is known that both naringin and salicylic acid have anti-carcinogenic effects on colon cancer (5, 6). However, the effect of two materials combined had not been investigated. In this study, it is found that both salicylic acid and naringin cause a decrease in the number of colorectal adenocarcinoma cells. The combination of naringin and salicylic acid also caused a decrease.

In addition, the results of MTT assay were better in 48th hour than in 24th hour. That shows that naringin and salicylic acid affect cancer cells more efficiently in this time period. However, 48 hours are also not enough to make a conclusion which supports the idea that naringin and salicylic acid affect more efficiently in longer periods.

The increase in apoptotic gene expression was exclusive. The expressions of *APAF 1*, *BAX*, *BCL2*, *BCL XL*, *CASP3*, *p21*, *p27* and *p53* increased. *p53* have a major importance in maintaining genome stability and integrity. It can lead cell cycle arrest and provide DNA repair. In addition, if the repair of the damage is not possible, then *p53* causes cell death via apoptosis (8). *BAX* is a cell death promoter protein (9, 10). As it has been suggested in the previous studies, the expressions of *p53* and *BAX* are higher in cancer cells than normal cells (8, 9, 10). It is also showed in this study. Therefore, these results are compatible with the literature. *APAF 1*, *CASP3*, *p21* and *p27* are also apoptosis inducer genes (11). Their expressions were increased especially in 200 μM concentration of naringin and salicylic acid combination. Therefore, the mixture of the molecules affects better. The increase in *CASP3* is also an indicator of damaged mitochondrial potential. *CYC C* is an important component of electron transport chain (11). The expression of *CYC C* increased especially in 100 μM concentration of naringin and salicylic acid combination. This indicates that mitochondrial membrane potential is damaged. The ratio of *BAX/ BCL2* is important while evaluating the mitochondrial membrane potential. The increase of these genes is distinct in the combination of naringin and salicylic acid. In addition, they do not increase proportionally. Therefore, it also indicates a damaged mitochondrial membrane potential.

Survivin is an apoptosis inhibitor gene (11). The expression of *survivin* especially decreased when treated with the combination of naringin and salicylic acid. When the concentration is increased from 100 μM to 200 μM, the decrease became more distinct. This shows that not only the combination of the molecules causes an increase in apoptosis inducer genes, it also causes a decrease in apoptosis inhibitor genes such as *survivin*.

The expression of genes which are members of antioxidant pathway such as *CAT*, *GPX*, *SOD* and *SOD2* were also studied. *CAT* plays a role in protection against oxidative stress (11). The increase in the expression of *CAT* indicates oxidative stress. The increase in *GPX* is also an indicator of oxidative stress, because *GPX* is a protector of cell against oxidative damage. The increase in *SOD2* is more than *SOD1*. This shows that naringin and salicylic acid are more effective on the expression of *SOD2*. *SOD1* and *SOD2* both destroy free superoxide radicals. *SOD1* converts free radicals to molecular oxygen and hydrogen peroxide whereas *SOD2* converts to diatomic oxygen and free radicals (11). *SOD1* is cytosolic whereas *SOD2* is mitochondrial (11). Therefore, it can be concluded that naringin and salicylic acid are more effective on mitochondrial antioxidant pathway. However, the expression of *SOD2* decreased when it is treated with 200 μ M of the combination. This is due to the mitochondrial damage which causes distraction and dysregulation of protein damage.

Although the study has reached its aims, time is a limitation factor because the results after 48th hour were not investigated. It needs to be examined in the further studies in order to explain the long period effects of naringin and salicylic acid.

As a result, it can be said that naringin, salicylic acid and especially their combination can be a promising treatment as a supported option for colon cancer patients in the future.

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Ethics Committee Approval: N/A

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THE RELATIONSHIP BETWEEN DIGIT RATIO (2D:4D) AND CARDIOVASCULAR CAPACITY IN YOUNG ADULTS

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ABSTRACT

Aims: The ratio of the second-to-fourth finger length was first proposed as a prenatal testosterone biomarker. Studying this matter with a different point of view, the aim of this study is to find whether there is a positive relationship between digit ratio and cardiovascular capacity.

Methods: The data of 82 students who were between the ages of 18 and 25 old from Trakya University Faculty of Medicine were analyzed by evaluating the results of the six-minute walking test and the results of their digit measurements. Independent Samples T-Test was used to determine the correlation between the prevalence of longer 4th digit and six-minute walking test results.

Results: The data obtained from the test results of the students, that were grouped regarding digit ratio, were statistically evaluated. With the results of the six-minute walking test, students that have lower digit ratio walked 593.87 ± 73.2 meters while students with higher digit ratio walked 584.17 ± 71 meters showing us that there is not a significant relationship between cardiovascular capacity and digit ratio.

Conclusion: With the gathered information and results, it is seen that there is not a positive relationship between digit ratio and cardiovascular capacity. In conclusion it can be said that digit ratio does not have a beneficial effect on a persons cardiovascular capacity. Usage of digit ratio as a prenatal hormone exposure has been increasing, and extensive studies in physiological and psychological conditions in humans have been correlated with digit ratio, including athletic ability, fertility, social behaviors, sex-biased diseases, and sexual orientation.

Keywords: Fingers, androgenization, testosterone,

INTRODUCTION

Recent studies show that prenatal testosterone exposure during the second trimester of gestation can be reflected in a person's digit ratio (2D:4D) (1). If the digit ratio is low, prenatal testosterone exposure is expected to be higher, making the 4th digit finger longer than 2nd. Human perinatal testosterone production consists of three distinct peaks, a mid-gestational peak, and two postnatal peaks. In these three distinct peaks, the mid-gestational peak is known to have an important biological effect on producing the differences between sex at birth. However, the sex differentiation may continue after birth (1).

Since peripheral blood cannot be drawn from a fetus in utero, researchers interested in studying the effects of perinatal testosterone had to rely on a variety of other methods (1). The use of finger or digit length ratio measurement of 2D:4D was proposed as a prenatal testosterone marker by John Manning et al (2) in 1998.

As mentioned before the lack of peripheral blood measurement from fetuses in utero is an important obstacle to the direct validation of 2D:4D or any adult marker for perinatal androgen action (1). However, there are other alternative methods for direct fetal androgen measurement that have been a useful research tool validating 2D:4D ratios such as amniotic fluid, neonatal cord blood, and gravid maternal blood.

In this study, our aim is to research whether there is positive relationship between digit ratio and cardiovascular capacity. To define cardiovascular capacity, six-minute walking test is used and linked with digit ratio, therefore it is expected that people with lower digit ratio have higher cardiovascular capacity which causes them to walk longer in given time.

MATERIAL AND METHODS

This study was approved by Scientific Researches Ethics Committee of Trakya University Medical Faculty. The study included 82 students from Trakya University Medical Faculty with the age range of 18 to 25, and carried out in Trakya University Physical Therapy and Rehabilitation Center from 19 to 29 June 2017. The study has an observational, descriptive and cross-sectional design. The sample size of 82 students was determined by performing power analysis.

The subjects are divided in 2 groups, as the ones with the digit ratio lower than 1 included to "lower digit ratio group", higher than 1 to "higher digit ratio group". 4th and 2nd digits length were measured from the most proximal crease to the finger tip using a caliper. To eliminate bias due to observational errors, all digits were measured by one researcher.

Considering the result of the power analysis, it was determined to have at least 41 participants in each group, thus first 41 participants with higher and 41 with lower digit ratio were selected for 6MWT after measuring their digits. Before and after 6MWT students heart rates were measured with a pulse oximeter. 6MWT provides information by measuring the distance (m) an individual is able to walk over a total of six minutes on a 60 meter long hard, flat surface, thus gives us information about a person's cardiovascular capacity. The obtained data were recorded and statistical analysis was performed.

Student t test was performed to compare both groups in regard to their pulse rates before and after 6MWT, also the average covered distance. As for descriptive statistics, mean \pm standard deviation and numbers were used. P value <0.05 is considered statistically significant.

RESULTS

In the present study, the population was composed of 82 students. Out of the total 82 students who were included in the study, 41 were with higher digit ratio and 41 were with lower digit ratio. Baseline demographics and physical characteristics of study subjects are demonstrated in Table 1.

Table 1: Baseline demographic and physical characteristics of the study subjects

	Higher Digit Ratio (n=41)	Lower Digit Ratio (n=41)	P value
Height	1.68 \pm 0.07	1.71 \pm 0.08	0.045
Weight	61.08 \pm 11.5	65.69 \pm 11.6	0.077
BMI	21.05 \pm 3.02	21.62 \pm 2.46	0.356

Data are represented as mean values \pm Standart Deviation (SD), BMI= Body Mass Index.

The average digit ratios are calculated as: 0.956 for lower digit ratio group, 1,027 for higher digit ratio group. The average the pulse values before and after walking, also the average distance of subjects are shown in Table 2. As the result of the performed statistical analysis, no statistically significant different between 2 groups were detected.

Table 2: Results of six-minute walking test (6MWT)

	Higher Digit Ratio (n=41)	Lower Digit Ratio (n=41)	P value
Pulse (before)	82.72 \pm 12.9	82.29 \pm 11.4	0.874
Walked (meter)	593.87 \pm 73.2	584.17 \pm 71	0.547
Pulse (after)	114.21 \pm 26.7	113.00 \pm 18.6	0.813

DISCUSSION

Our aim in this study was to elucidate the effect of digit ratio (DR) on a person's cardiovascular capacity. It was expected that students with lower digit ratio would walk longer in 6MWT which shows the person's cardiovascular capacity. The results did not show us a statistically significant difference between students with higher and lower DR hence, however students with higher DR walked longer than students with lower DR despite having higher BMI and lower pulse after 6MWT.

It was found that in mice 4th digit has higher androgen receptor and estrogen receptor α (ER- α) activity than 2nd digit (3). If the androgen receptor activity is lower, 4th digit tends to grow less which causes a higher DR (3). Whereas, inactivation of ER- α causes a higher growth on 4th digit (3). However, development mechanism of digit ratio still remains unknown in humans. In 1998 digit ratio was concerned as a prenatal testosterone biomarker, a study showed us that men with lower 2D:4D ratio had lower estrogen and higher serum testosterone, which lead to a hypothesis that people with lower 2D:4D had a higher prenatal testosterone exposure than people with higher 2D:4D making their 4th digit longer (2).

In our study, DR was correlated with cardiovascular capacity and was expected to be seen whether people with lower DR have the higher cardiovascular capacity. Similar researches were not found like ours, however, with the gathered information it was seen that DR corresponded with sports performances (4). In the study of M. Bennet et al. (5) found that rugby players with lower DR had better performances. Also Frcik NA et al. (6) found out that basketball players that have lower left 2D:4D achieved higher competitive standards. In other researches it was seen that professional football players had lower 2D:4D ratios and compared to males with higher DR, men with lower DR acquired higher attainment in variety of sports and had higher mental rotation scores (a measure of visual-spatial ability) (7). The only research that can be associated with was done by Longman D et al. (8) comparison of digit ratio with rowing that needs a more developed cardiovascular system and higher power output. Unlike our results, they found significant negative correlations between male digit ratios and 2,000 m ergometer performance. This shows that prenatal testosterone exposure can have a long-term effect on a person's traits associated with physical power in males.

As previously stated DR is used for other purposes as well. For example, it is seen than heterosexual women are exposed to less prenatal androgen exposure than homosexual women, also men that are exposed to more prenatal androgen than their older brother are more likely to be homosexual in their adulthood (9). DR can have an effect on social behavior (10) and fertility (11) as well. On the other hand, digit ratio is also used as an indicator for some sex-biased disease (12, 13), such as; infertility, autism, dyslexia, migraine, stammering, immune dysfunction, myocardial infarction and breast cancer. Additionally, DR can be a base

to further expand the knowledge in numerous scientific researches.

Even though expected amount of people were reached, limitation factor was that 6MWT may not be enough to determine a person's cardiovascular capacity, for better results more options can be used. For instance, increasing the number of measured students and with the 6MWT, usage of exercise electrocardiogram may give more reliable results. Furthermore, expanding the measurement system may lead us to accomplish better results.

Ethics Committee Approval: This study was approved by Scientific Researches Ethics Committee of Trakya University Medical Faculty.

Informed Consent: Verbal informed consent was obtained from the participants of this study.

Conflict of Interest: The authors declared no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

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ASSESSMENT OF PATIENT SATISFACTION OF IMPLANTABLE VENOUS PORT CATHETER USE: A SURVEY-BASED STUDY

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ABSTRACT

Aims: Implantable venous port catheter is a widely used clinical tool with plenty of objectives such as parenteral nutrition, taking blood sample, management of medicines used in chemotherapy. The aim of this study is to evaluate patient satisfaction regarding implantable venous port catheter for chemotherapy treatment.

Methods: The data of 19 patients operated from March 2017 to June 2017 were analyzed as a survey based assessment in Trakya University Hospital Department of Thoracic Surgery. Age, gender, satisfaction of having an implantable venous port catheter, the level of pain during implantation, being informed before the operation, fear of having a complication due to the implantable venous port catheter, being uncomfortable about having an implantable venous port catheter and not liking the appearance of implantable venous port catheter were included on the survey. The type and stage of cancer, comorbidity and the vein which is a port catheter was implanted in were recorded from patient charts.

Results: The mean age of participants was 61.44 ± 7.493 years. Out of all 10 (52.6%) were male and 9 (47.4%) were female. The most utilized side during insertion was right jugular vein (94.4%). Rectum cancer was the most diagnosed cancer type with six patients. The most seen cancer stage was found to be stage-4-IV (66.7%). Comorbidity was detected in 15 patients (83.3%). 89.5% of patients had indicated that they were informed enough before the procedure. 57.9% of the patients responded to question of fear of complication as "yes". According to these responses, 52.6% of the patients emphasized their discomfort as "little".

Conclusion: This survey-based assessment study points out that most of the cancer patients are contented for being implanted with an implantable venous port catheter. Having an implantable venous port catheter is safer and easier way for cancer patients. Moreover, it gives patients more freedom of movement.

Keywords: Port catheter, patient satisfaction, survey

INTRODUCTION

Implantable venous port catheter (IVPC) is a widely used clinical tool with plenty of objectives such as parenteral nutrition, taking blood sample, management of medicines used in chemotherapy (1, 2). It is implanted in subcutaneous localization under local anesthesia (3). Subclavian vein or internal jugular vein are commonly preferred for implantation (4). IVPC is particularly applied to intermittent, long-term cancer patients (5). It has been reported that using IVPC on chemotherapy patients prevents venous toxicity caused by constantly

opening venous channels (1). IVPC is an easier procedure for the patients because it is implanted under local anesthesia, promotes administration of chemotherapy, does not need special care, reduces pain and it does not require constantly opening venous channels (3, 5, 6). Nevertheless, using IVPC can cause some problems. The most encountered complications are migration of catheter, infection and venous thrombosis (5). Furthermore artery puncture, pneumothorax, hemothorax, intravascular embolisms are also among the observed complications (5, 7).

The aim of this study is to evaluate patient satisfaction regarding IVPC usage who came to Trakya University Faculty of Medicine Department of Thoracic Surgery between 20 March and 01 June 2017 in order to administrate catheter for facilitation of their chemotherapy treatment.

MATERIAL AND METHODS

This study was approved by Trakya University Faculty of Medicine Scientific Researches Ethics Committee. In this study, the data of 19 patients operated from March 2017 to June 2017 were analyzed with a survey based assessment in Trakya University Hospital Department of Thoracic Surgery.

Firstly, the patients with IVPC who volunteered to be in the study. The survey was filled after the IVPC operation of cancer patients. As appeal to hospital and demographic data; age, gender, satisfaction of having IVPC, the level of pain during implantation of the port catheter, being informed before the operation, fear of having a complication due to IVPC, being uncomfortable about having it and being disturbed by the appearance of IVPC were included on the survey (Table 1). In addition, the type and stage of cancer, comorbidity and the vein which is IVPC was implanted in were recorded from patients' charts.

Table 1: The questions in the survey

1) Age	
2) Gender	Male () Female ()
3) Are you satisfied with the implantation of port catheter?	Yes () No ()
4) Grade the pain that you feel during the implantation of the port catheter?.	1: None 2: Little 3: Partially 4: Pretty much 5: Intense
5) Are you informed enough before the implantation?	Yes () No ()
6) Are you afraid of having any complication due to port catheter?	Yes () No ()
7) Grade how much you are disturbed by having a port catheter and how often you think about it.	1: None 2: Little 3: Partially 4: Pretty much 5: Too much
8) Grade how much you are disturbed by the appearance of port catheter.	1: None 2: Little 3: Partially 4: Pretty much 5: Too much

Since this study is based on descriptive statistics, continuous variables are expressed as mean \pm standard deviation and categorical variables are expressed as numbers and percentages. All statistical analyses were performed using SPSS.

RESULTS

This survey-based study was conducted among 20 patients inserted IVPC in Trakya University Faculty of Medicine, Department of Thoracic Surgery. One patient was excluded due to missing data so, 19 patients were included in the study.

The mean age of participants was 61.44 ± 7.493 years. Out of all 10 (52.6%) were male and 9 (47.4%) were female. The most utilized side during insertion was right jugular vein (94.4%). Different types of cancer such as rectum, breast, colon, pancreas, stomach and larynx have seen among the patients and rectum cancer was the most diagnosed cancer type with six patients. Furthermore, the most common cancer stage was found as stage-4-IV (66.7%). Comorbidity was detected in 15 (83.3%) patients. 89.5% of patients had indicated that they were informed enough before the procedure. However, 57.9% of the patients responded to question of fear of complication as "yes". 52.6% of the patients defined their discomfort as "little". Moreover, the distribution of patients' answers to the question which is about the disturbance of appearance of port catheter was shown in Figure 1.

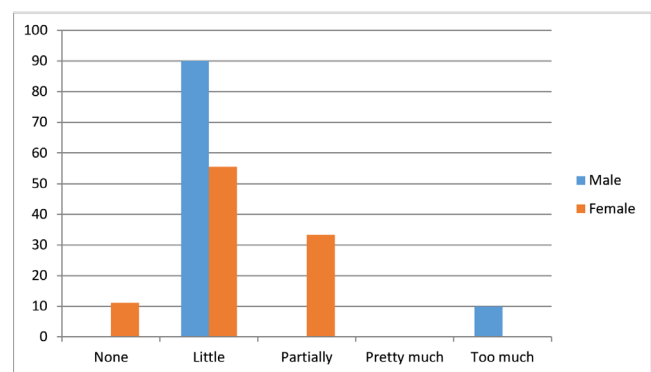


Figure 1: The distribution of answers to the question 8

Likewise, the grade of the pain that was felt during the implantation of port catheter was indicated in Figure 2. With all the results considered, it was found that 100% of the patients were satisfied.

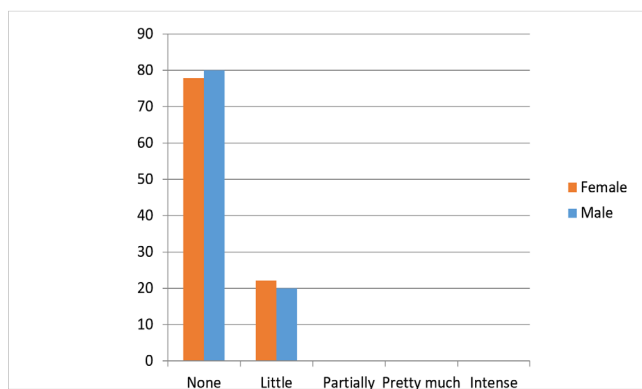


Figure 2: The grade of the pain that was felt during the implantation of the port catheter

DISCUSSION

Researchers commonly focus on complications due to its usage. However, evaluating patient satisfaction and quality of life regarding catheter usage are crucial issues. A survey-based assessment conducted by Nagel et al. (6) has reported that negative effects of using the port catheter have low effects on daily life and also IVPC increased the patient satisfaction. In addition, a questionnaire-based survey conducted by Kreis et al. (7) has emphasized the significance of informing the patients before implantation of the port catheter.

Indwelling catheters are appliances of great rank broadly used in the administration of chemotherapy to cancer patients worldwide (8). They provide comfort, accessibility and safety in the application of chemotherapy, which when managed by peripheral vein, may generate complications, such as pain, phlebitis, skin necrosis and compartment syndrome (9). In an effort to explain the satisfaction of cancer patients that are having port catheters, a questionnaire was conducted among 19 patients who had IVPC implantation.

In this study, 100% of the patients said that they were “satisfied” to have a port catheter. The reason for this may be that patients prefer one time needle insertion instead multiple needle insertions. Furthermore, chemotherapy takes less time with catheter. Moreover, some patients can be treated at their homes with chemotherapy pump via IVPC. It provides long-term accessibility which is preferred for cancer patients who get chemotherapy for years. Including both male and female patients, 78.9% of 19 people selected “little” from the questionnaire for the pain that they felt during the catheter insertion. In addition, in the study of Nager et al. (7) the pain of insertion was found to have no effect on patient satisfaction. Mo-

reover, fear of complication is rated as “a little bit” in the questionnaire of the study of H.Kreis et al. (6) and also in the same study it is reported that “a little bit” choice for pain of implantation is the remarkable result which is similar to our study. The results of this study and other recent studies show that implantation of the port catheter is not an extremely painful process for the patients.

In addition, port catheters are mostly inserted to right jugular vein. The jugular vein is preferred because it is extremely close to the skin and simple to locate with ultrasound. It runs straight down to the heart and has the lowest risk for problems during placement of the catheter (10). As it is shown that in the study of Nagel et al. (7) 83.7% of the population has right jugular vein inserted port. Our data reveals that 94.4% of the patients has right jugular vein inserted port when compared with Nagel’s study.

The percentage of the patients who stage 4-IV cancer is 63.2%. According to these consequences, in the patients who have attended this study, IVPC is mostly used for cancer stage 4-IV. Moreover fear of complication is another encounter that the patients had to face.

In current literature, there are a lot of examples for complications in catheter placement (6). In this study, 57.9% of the patients are having fear of complication. Even 89.5% of the patients thought that they were informed enough before the procedure, they are still afraid of complication. It is found that 44.4% of the patients are overall satisfied with IVPC in the research of H.Kreis et al. (6), but in our study satisfaction of the patients revealed 100%.

As a conclusion, this survey-based assessment study points out that most of the cancer patients are contented for being implanted with a port catheter. Having an IVPC is safer and easier way during treatment and follow up period for cancer patients. Moreover, it gives more freedom of movement.

Although, the survey has reached its aims, the small number of patients might limit our conclusion. However, further studies including more patients and long term follow-up intervals are needed.

Ethics Committee Approval: This study was approved by Scientific Researches Ethics Committee of Trakya University Medical Faculty.

Informed Consent: Written informed consent was obtained from the participants of this study.

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A RARE CASE FOR AWARENESS: METAPLASTIC CARCINOMA OF BREAST

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ABSTRACT

Aims: Metaplastic breast carcinoma is an infrequent kind of breast carcinoma, more aggressive and has poorer prognosis than other breast carcinomas. With this case report, we aim to reveal pathologic and clinical features of the metaplastic breast carcinoma and its similarities to ductal invasive carcinoma. However its differentiation is possible and should not be skipped in diagnosis.

Case Report: A BIRADS category of 4c mass that measured 38x31 mm in the ultrasonography was detected in a 71-year-old female patient who applied with a complaint of a palpable mass under the right areola. The result of biopsy was interpreted morphologically as spindle cell proliferation containing necrosis. Thereafter, the mass was excised with simple mastectomy. The results of the immunohistochemical examination of the tumor with the diameter of 6 cm revealed progesterone receptor, estrogen receptor and HER2 to be negative, p63 staining to be positive. The mass was histopathologically diagnosed as metaplastic carcinoma with well differentiated squamous cell and malignant mesenchymal component (osteosarcomatous area).

Conclusion: Metaplastic breast carcinoma which resembles invasive ductal carcinoma with general characteristics is differentiated from invasive ductal carcinoma with larger tumor size, less lymph node involvement, less hormone receptor positivity. In order to prevent the delay of diagnosis, invasive ductal carcinoma should be considered in the definitive diagnosis in the elderly patients. Treatment should be started immediately and followed closely because of the high risk of local recurrence.

Keywords: Carcinoma, breast cancer, simple mastectomy

INTRODUCTION

Metaplastic breast carcinoma (MBC) which makes up all less than 1% of malignant breast lesion formations, is a rare high grade lesion (1-4). Huvos et al. (1) first introduced the term metaplastic carcinoma in 1974. The incidence of MBC which includes both of epithelial and mesenchymal components is increasing gradually. The late inclusion of MBC in pathological assortment is effective in this increasing.

Although it has the same clinical findings of invasive ductal carcinoma (IDC), it might give the similar sign of inflammatory breast cancer. MBC is observed in the 5th decade like IDC (5). The youngest case is 16 years old (2, 3). The foundation of approaching patients diagnosed

with malignant breast carcinoma should be based on the individual and type of carcinoma.

CASE REPORT

A 71-year-old female patient with palpable mass under the right areola, applied to an external center. During ultrasonography (USG), cystic degenerated hypoechoic lesion with the size of 38x31 mm, with lobulated contour featured was identified on the right upper outer dial retroareolar field of the breast. The lesion is classified as category 4c according to Breast Imaging Reporting and Data Systems (BIRADS) and tru-cut biopsy was applied to that lesion. During biopsy, lying ductal structures and

squamous looking small islets were detected inside the fibromyxoid-looking stroma. The human epidermal growth factor receptor 2 (HER2), progesterone receptor (PR), estrogen receptor (ER) were evaluated as a negative (triple negative) carcinoma on histopathological examination. Positive staining was observed in ductal structures with E-cadherin and p63 staining and also in the epithelial field with CK 5-6 staining. Furthermore, a slight increase was found with Ki-67 staining. Consultation had been asked from Trakya University Faculty of Medicine, Department of Pathology Laboratory. According to immunohistochemical examination of Trakya University Faculty of Medicine, Department of Pathology Laboratory, P63 scrapper chain and actin were detected as negative and Ki-67 index was detected as low (Figure 1).

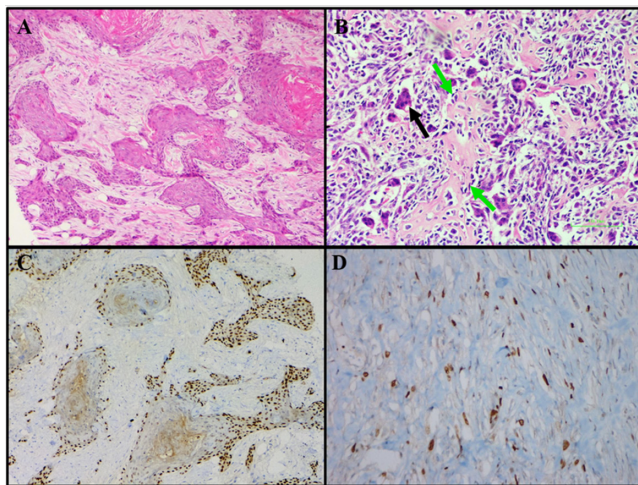


Figure 1: A. Squamous-looking islets in fibromyxoid stroma (H+EX40) B. Supporting the diagnosis of malignant mesenchymal component, osteoclast-like giant cells (black arrow), osteoid matrix and osteoblast cells (green arrow) containing osteosarcomatous component (H+EX100) C. Positive staining pattern with p63 at basal level of squamous islands (p63X100) D. Ki67 immunoreactivity in 20% of the mesenchymal component (Ki67X200)

Morphological identification was interpreted as “the spindle cell proliferation that contains necrosis”. Metaplastic carcinomas and the lesions such as cellular stromal fibroadenoma, phyllodes tumor, primary mesenchymal tumors of the breast and fibromatosis were considered for definitive diagnosis. Excision of the lesion was recommended because accurate description cannot be possible on the tru-cut biopsy.

As a result of thorax computed tomography (CT) and positron emission tomography (PET) (Figure 2), multiple lymphadenopathies were detected in the right paratracheal region and also a few lymphadenopathies which have 10 mm diameter were detected in left para-aortic area and 5 mm diameter in right hilar region. All lymphadenopathies were evaluated as having metastatic character. Increased fluorodeoxyglucose (FDG) involvement on the 1 cm, subpleural nodule which is located on left upper anterior lobe of lung, was evaluated as a malign lesion. The mass which was identified as BIRADS category 4c according to the USG results of the external center was identified as BIRADS category 5 according to USG and mammography at Trakya University Faculty of Medicine.

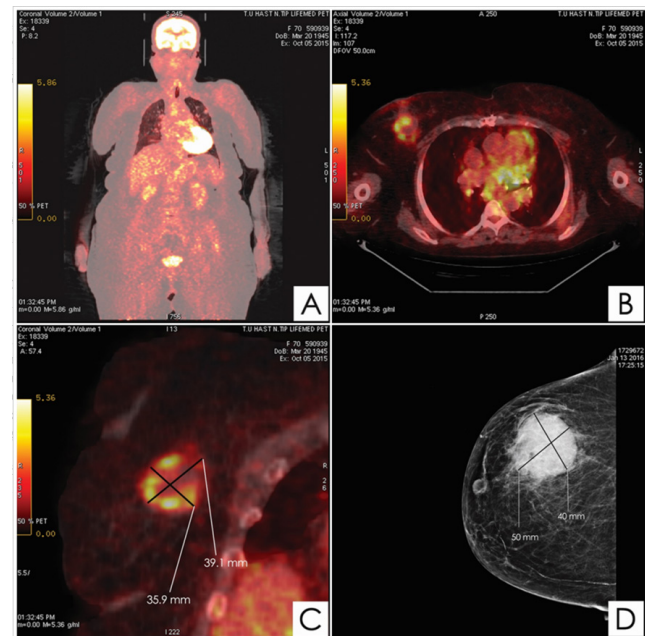


Figure 2: PET and mammography images of the patient A. Increased FDG uptake (involvement) assessed as lymph node metastasis B. and C. Increased FDG uptake (involvement) in the breast D. Mass appearance in mammography

After all examinations, simple mastectomy was applied to patient. Tumor was not detected in the right axillary lymph node biopsy which was taken by frozen. Therefore, sentinel modified radical mastectomy (MRM) were excluded from the process. On histopathological examination of the mastectomy; the tumor with a maximum diameter of 6 cm was consisted of well differentiated squamous cell carcinoma and malignant mesen-

chymal component (osteosarcomatous area). Therefore, histologic diagnosis was metaplastic carcinoma. In addition, in TNM stage it was identified as pT3, pN0, pMx because the largest size of the tumor was higher than 5 cm and there were no remote organ metastasis and lymph node involvement.

DISCUSSION

Since MBC was not recognized as a specific pathologic diagnosis until 2000, doctors had limited information about patients' demographic information, presentation, tumor characteristics and treatment modalities. Up to the present, the factors that differ MBC from more prevalent malignant breast histologic features, have been attempted to be familiarized only with small series and case reports.

Metaplastic carcinoma of the breast, which includes malignant mesenchymal and malignant epithelial tissue components with biphasic lesions, is a general term that describes the heterogeneous group (Table 1). Heterogeneity is increasing in malignant breast lesions and this condition depends on many factors such as hormone receptor expression, changing gene expression and histologic appearance.

Table 1: MBC classification according to the components it contains

World Health Organization (WHO) 2003 Metaplastic Breast Carcinoma Classification	
Pure epithelial metaplastic carcinoma	Mixed epithelial/mesenchymal metaplastic carcinoma
<ul style="list-style-type: none"> • Squamous cell carcinoma • Cord cell metaplasia adenocarcinoma • Adenosquamous carcinoma • Mucoepidermoid carcinoma 	<ul style="list-style-type: none"> • Chondroid metaplasia carcinoma • Osseous metaplasia carcinoma • Matrix-producing carcinoma

Most of the metaplastic carcinomas are occasional, but there may be a trace of tendency to metaplastic spindle cell carcinoma developed from pre-existing lesions, including papillomas, complicated sclerosing lesions and nipple adenomas (6).

The most important prognostic factor is the tumor size and phase. Tumor size can change between 0.8-12 cm (av. 3 cm) (2). Size being less than 4 cm is a good prognosis sign (3). Spread of the MBC to other parts of the body often occurs by blood circulation or rarely

through the lymphatic circulation. The most common regions of metastasis are lung and bone (2, 3). There is no specific finding in mammography and ultrasound imaging (5).

Table 2: At the table below Pezzi et al. (6) used National Cancer Data Base of 892 MBC and 255.164 IDC cases. According to this ratio, ER, PR values are negative in the vast majority of MBC patients while IDC patients' values are positive. Nodal involvement is high in both of cancer types. The tumor size is less than 2 cm in more than half of IDC patients. Tumor size is between 2 to 5 cm in nearly half of MBC patients.

	Metaplastic Breast Carcinoma	Infiltrative Ductal Carcinoma
Mean age	61,1	59,7
Tumor size		
<2 cm	29.5%	65.2%
2-5 cm	49.6%	29.5%
>5 cm	20.4%	5.2%
Estrogen receptor status		
Positive	11.3%	74.1%
Negative	88.7%	25.9%
Progesterone receptor status		
Positive	10.4%	62.4%
Negative	89.6%	37.6%
Nodal status		
Positive	78.1%	65.7
Negative	21.9%	34.3

Metaplastic breast carcinoma which has similar clinical features with IDC, is usually considered to be a high grade carcinoma (Table 2). Despite this, it may rarely give similar evidence of inflammatory carcinoma (2, 3, 6).

A difference was seen in MBC patients in comparison with IDC patients due to race/ethnicity. MBC patients are mostly Afro-American or Hispanic. The reason for these variations is unknown, however these ethnic groups represent low but increased risk for MBC (7).

Invasive ductal carcinomas are diagnosed earlier than MBC. Since MBC has a faster and more aggressive growth, it is relatively rarely seen. Therefore, its diagnosis can be skipped easily and it can be confused with be-

nign lesions during imaging.

Lim et al. (8) have been classified 51 MBC patients whether they have ER, PR and HER2 expression. Being negative for all three receptors have been interpreted as worse prognosis.

By comparison with IDC; ER, PR and HER2 oncogene expressions are lower and Ki-67 and p53 oncogene expressions are higher in MBC. Literature-based studies identify the ratios as 35% for HER2 positivity and 0% for MBC in high grade (grade 3) breast carcinoma. ER and PR positivity have been reported as a percentage between 0% and 25% in the literature (2, 7). After performed studies, low hormone receptor positivity has generally been characterized for MBC therefore, the treatment approaches have changed. Thereby, hormones or anti-HER2 treatment are less successful on these patients. In MBC, extreme expression of p63 gene is also known (8).

Although some studies have reported that breast-conserving therapy and modified radical mastectomy conclude with the same results, having large size of tumor and the risk of local reoccurrence for the first 2-5 years being between 35% and 62% increase the propensity to MRM (3, 5). Respectively MRM, Radiotherapy (RT) and systemic chemotherapy (CT) are applied in usual treatment protocol. After evaluating 27 patients with results of different chemotherapy studies from Clinic of Mayo for 30 years, Rayson et al. (9) have been reported that systemic CT has low effect. Low incidence of MBC's lymphatic spread can explain its resistance to traditional CT agents and sensitivity of RT.

In our case, squamous cell carcinoma in the epithelial component and carcinoma including osteosarcomatous field in the mesenchymal component are present. The patient applied with a complaint of a palpable mass that was measured as 6 cm in diameter which is over the 4 cm specification of bad prognostic determination stated in literature. During histopathologic examination, prognostic factor TN was tracked. In addition, p63 staining was positive. Since the case is classified as category 5 according to BIRADS classification, it was highly doubted and advanced diagnosis methods were applied. In many studies, the risk of metastasis to axillary lymph nodes has been reported as high. However, in our case, the patient was diagnosed with MBC has no axillary metastasis. Therefore, MRM was not implemented and simple mastectomy surgery was applied.

Acknowledgement:

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Ethics Committee Approval: N/A

Informed Consent: Written informed consent was obtained from the participant of this study.

Conflict of Interest: The authors declared no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

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Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments
1. Grant					
2. Consulting fee or honorarium					
3. Support for travel to meetings for the study or other purposes					
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like					
5. Payment for writing or reviewing the manuscript					
6. Provisions of writing assistance, medicines, equipment, or administrative support					
7. Other					

*This means money that your institution received for your efforts this study.

Section 3. Relevant financial activities outside the submitted work.

Please indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information in the white boxes.

Relevant Financial Activities Outside the Submitted Work

Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments
1. Board membership					
2. Consultancy					
3. Employment					
4. Expert testimony					
5. Grants/grants pending					
6. Payment for lectures including service on speakers bureaus					
7. Payment for manuscript preparation					
8. Patents (planned, pending or issued)					
9. Royalties					
10. Payment for development of educational presentations					
11. Stock/stock options					
12. Travel/accommodations/meeting expenses unrelated to activities listed**					
13. Other (err on the side of full disclosure)					

*This means money that your institution received for your efforts.

**For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section 4. Other Relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

No other relationships/conditions/circumstances that present a potential conflict of interest.

Yes, the following relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, we ask that you update your disclosure statements if anything has changed. On occasion, we may ask you to disclose further information about reported relationships.

This form is adapted from the Author Disclosure Form created by the International Committee of Medical Journal Editors (ICMJE). The ICMJE has not endorsed nor approved the contents here. The official version of the ICMJE Author Disclosure Form is located at

http://www.icmje.org/coi_disclosure.pdf



CONSENT FORM for CASE REPORT

Title of Project: _____

1. I have read, and understood the Participant Information Sheet dated _____
2. I freely agree to the use of my medical records for the purpose of this study.
3. I understand that the case report will be published without my name attached and researchers will make every attempt to ensure my anonymity. I understand, however, that complete anonymity cannot be guaranteed.
4. I have been given a copy of the Participant Information Sheet and Consent Form to keep.

Name of Participant _____

Signature of Participant _____ Date _____

The participant was informed through phone call and a verbal consent was obtained.

The following section regarding the witness is not essential but may be appropriate for patients where the research teams feel that the participant should have a witness to the consent procedure.

Name of witness (if appropriate) _____

Signature of witness _____ Date _____

Name of Researcher _____

Signature of Researcher _____ Date _____

Name of Researcher _____

Signature of Researcher _____ Date _____

