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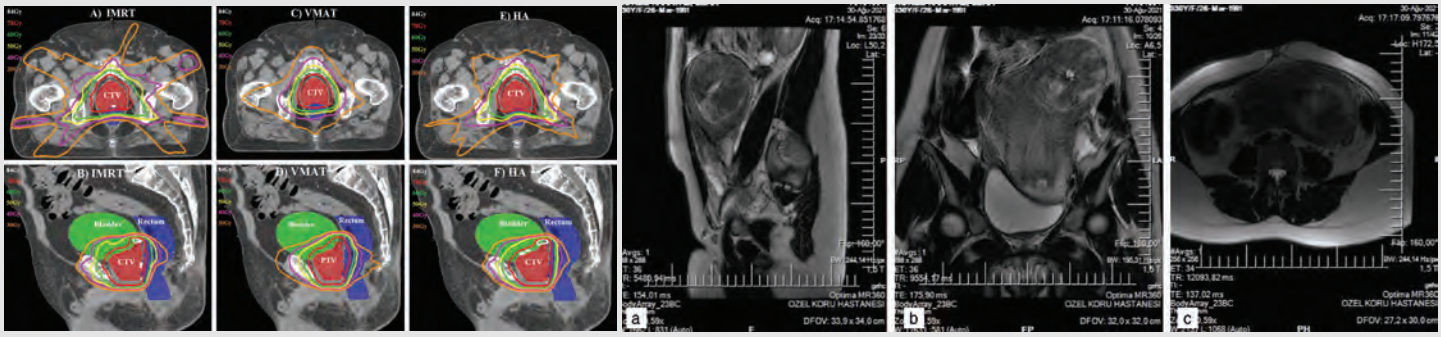

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Official Journal of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital

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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables.

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Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

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Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press;2005.

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Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

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CONTENTS

ORIGINAL ARTICLE

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The Contribution of Curative Dose Radiotherapy to Primary Disease with Concurrent Chemotherapy on Survival in Patients with Metastatic Esophageal Cancer

Menekşe Turna, Meltem Kırlı, Okan Özdemir, Hamit Başaran, Kadriye Ayşenur Arlı Karaçam

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Abstract

Objective: Chemotherapy (CT) is the standard treatment for patients with metastatic esophageal cancer. Primary tumor progression is one of the important reasons for morbidity and mortality. Several studies have shown that aggressive treatment of primary tumors in metastatic patients may contribute to survival. In this study, patients with metastatic esophageal cancer and who received radiotherapy (RT) to the esophagus were evaluated.

Methods: Patients with metastatic esophageal cancer treated with esophageal RT were retrospectively evaluated. ECOG 3-4 patients were not included. Analyzes were performed with SPSS 22.0 (SPSS Inc., IBM Corp., Armonk, NY). Kaplan-Meier, Log-rank, and Cox-regression tests were used for the analysis.

Results: Forty-seven patients between 2009 and 2016 were evaluated. The median age was 61 (44-85); 60% of the patients were female. Eighty-nine percent of the histological subtype was squamous cell carcinoma. The mean RT dose was 45 Gy (20-68 Gy). Thirty percent of the patients had concurrent CT. The median overall survival (OS) was 14 months. 45 Gy and higher RT doses and concurrent CT were associated with better OS in univariate analysis (p=0.009, p=0.03). The median OS was nine months in patients receiving <45 Gy, and 20 months in patients who received RT ≥45 Gy; 24 months in patients who received concurrent CT, and 13 months in patients who did not. There was no significant prognostic factor in multivariate analysis.

Conclusion: Forty-five Gy and higher dose RT with concurrent CT after standard treatment may contribute to survival in metastatic esophageal cancer patients with good performance scores.

Keywords: Esophageal cancer, metastasis, radiotherapy, chemoradiotherapy

INTRODUCTION

Esophageal cancer ranks seventh in terms of incidence (604,000 new cases) and sixth in overall mortality (544,000 deaths) (1). East part of Turkey has the highest rates of esophageal cancer in the country and forms the bulk of daily oncology practice (2,3). According to the surveillance, epidemiology, and end results (SEER) data, 40% of the cases were diagnosed with the metastatic stage. Even if initially diagnosed as localized disease, the 5-year survival rate is below 50% (4).

Chemotherapy (CT) is the standard treatment approach for patients with metastatic esophageal cancer. However, survival rates are low. Primary tumor progression is one of the critical reasons for morbidity and mortality. Aggressive treatment of primary tumor in metastatic patients may contribute to survival. The best evidence for local radiotherapy (RT) for metastatic disease comes from prostate and nasopharyngeal cancer (5-7).

We, therefore, examined retrospectively survival outcomes associated with RT ± CT among patients with initially diagnosed

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metastatic esophageal cancer. We examined whether or not definitive dose RT with concomitant CT improves overall survival (OS) in patients presenting with metastatic esophageal cancer.

METHODS

We included patients with esophageal cancer who were metastatic stage at the time of diagnosis and confirmed histo-pathologically. All patients were staged with diagnostic endoscopy, radiological imaging including computed tomography scan of the chest, abdomen, and pelvis, and/or 18-fluoro-deoxyglucose positron emission tomography scan. All patients were classified according to the seventh edition of the American Joint Committee on Cancer staging manual. The patients were first treated with CT, and referred to the radiation oncology department for RT. Patients with stable disease and who had complete or partial responses were evaluated for RT. ECOG 3-4 patients were excluded from the study.

The treatment decision (RT doses and CT schema) was made by the treating physician. Patients were divided into three subgroups according to the treatment they received. Group 1 consisted of patients receiving just RT with a total dose of 30 Gy in ten fractions, which is generally applied as palliative doses. Group 2 consisted of patients receiving only RT with curative doses ≥45 Gy in 25-28 fractions. Group 3 consisted of patients receiving RT with curative doses combined with CT. Target volumes are defined according to the pre-CT scanning. All radiologically positive lymph node areas and primary lesions were included in the field. Elective lymph nodes were not treated. Local treatments for metastatic sites were not included in the analysis. After RT, the patients underwent regular clinical assessments and follow-up scans with 3-4 months of time-intervals for an objective assessment of the response. OS was the main objective and was defined as the time from diagnosis until death from any cause.

Statistical Analysis

All data were evaluated with SPSS 22.0 (SPSS Inc., IBM Corp., Armonk, NY). The Kaplan-Meier test was used for survival analysis. The Log-rank test and the Cox-regression test were used for the univariate analysis and multivariate analysis, respectively. The p value of less than 0.05 was considered statistically significant.

RESULTS

Forty-seven patients who were diagnosed with synchronous metastatic esophageal cancer and referred to the radiation oncology department for esophageal RT between 2009 and 2016 were evaluated. Sixty percent of the patients were female, and 40% were men. The median age of the patients was 61 (44-85) years. The most common metastatic sites were the liver, lung, distant lymph nodes, and bone. All patients were polymetastatic and without visceral crisis. Eighty-nine percent of the histological subtype was squamous cell carcinoma. Forty-seven percent of the tumors were located proximally, and the rest were located distally. The ECOG performance distribution of the patients was ECOG 0 in 3 (6%) patients; ECOG 1 in 10 (21%) patients and ECOG 2 in 34 (72%) patients. The distribution of T stage of the primary tumor was T2 in 1 (2%) patient; T3 in 40 (85%) patients, T4a in 3 (6%) patients; and T4b in 4 (7%) patients. The distribution of the N stage of the primary tumor was N1 in 2 (4%) patients; it was N2 in 12 (26%) patients, and N3 in 33 (70%) patients.

All patients had completed the CTs (2-6 cycles) for metastatic esophageal cancer. Cisplatin fluorouracil or paclitaxel carboplatin combination was used. RT was applied to 73% of patients with 2D-conventional and 27% of patients with the 3D-conformal method. The mean RT dose was 45 Gy (20-68 Gy). Fifty-one percent of the patients were Group 1 patients who had palliative doses (lower than 45 Gy, hypo-fractionation); 25% of the patients were group 2 who received a curative dose (45 Gy and higher, conventional fractionation) RT. Patients with group 3 who received concurrent CT were 24% of all patients. Concomitant CT regimens were 2 area under the curve carboplatin and 60 mg/m^2 paclitaxel weekly or cisplatin 60 mg/m^2 and 5-fluorouracil 1.000 mg/m^2 every 3 weeks.

All patients completed RT as planned. Patients who were given concurrent CT also completed their treatment without interruption. There were no patients who interrupted treatment due to treatment toxicity in our study. Mild esophageal toxicity was experienced in 39 patients; of 32 side effects 9 (23%) were grade 1 and 30 (77%) were grade 2. The median OS was 14 (5-74) months. Older age (≥65 years old), ECOG performance status, anatomical location of the tumor, T and N stages were not associated with survival outcome ($p<0.05$) in the univariate analysis (Table 1). 45 Gy and higher RT doses and concurrent CT applications were associated with better OS in the univariate analysis ($p=0.009$, $p=0.03$) (Figure 1A). One-year OS was 43% in patients receiving lower than 45 Gy and 56.5% in patients who received RT over 45 Gy, and the median OS was nine months and 20 months, respectively (Figure 1B). Median OS was 24 months in patients who received concurrent CT and 13 months in patients who did not (Figure 1C). There was no significant prognostic factor in multivariate analysis ($p<0.05$) (Table 1).

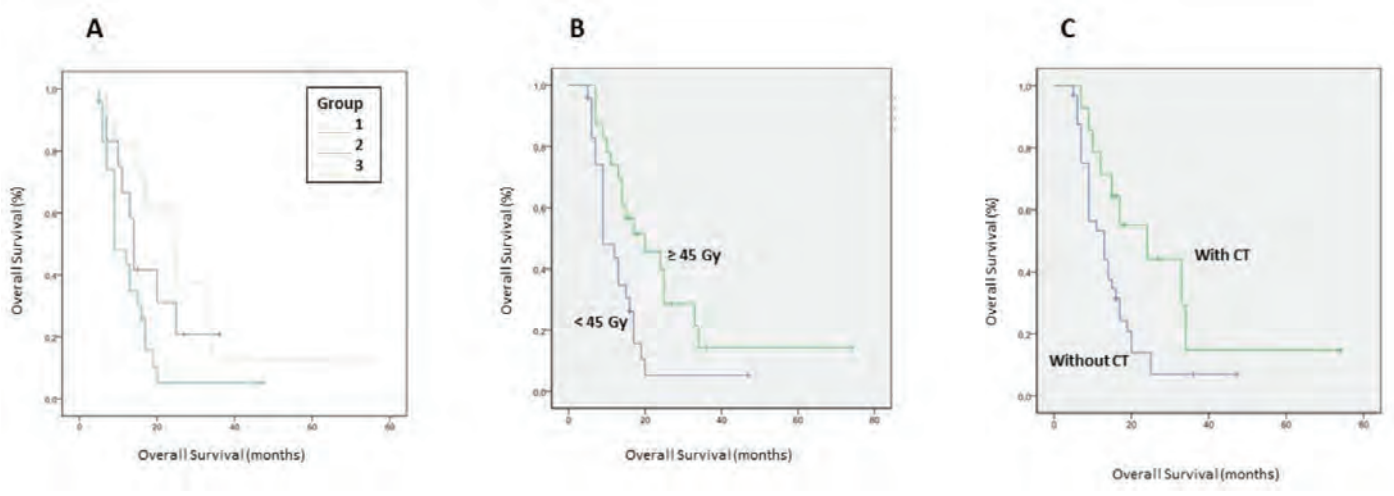

Figure 1. Overall survival curves according to the treatment groups (A), overall survival curves according to the RT dose groups (B), overall survival curves according to the concomitant CT status (C)

RT: Radiotherapy, CT: Chemotherapy

Table 1. Univariate and multivariate analysis of variables affecting overall survival

	p*	p**	95% confidence interval
Age group ≤65 >65	0.491	0.677	0.410-10.784
ECOG ECOG 0 ECOG 1 ECOG 2	0.219	0.869	0.408-7.477
Pathology group Squamous cell carcinoma Adenocarcinoma	0.032	0.088	0.841-12.214
Tumor location Upper Lower	0.377	0.839	0.452-1.906
T stage T2 T3 T4	0.291	0.600	0.693-1.953
N stage N1 N2 N3	0.561	0.601	0.315-1.953
RT dose group <45 Gy ≥45 Gy	0.009	0.642	0.157-10.346
Concomitant CT group Yes No	0.033	0.453	0.121-3.672
Treatment modality Palliative Radiotherapy Chemoradiotherapy	0.028	0.948	0.186-6.270

*Log-rank test, **Cox regression test, RT: Radiotherapy, CT: Chemotherapy

DISCUSSION

In this retrospective study, we found a significant improvement in OS with definitive dose RT to the primary tumor and concurrent CT in metastatic esophageal cancer patients. The standard treatment is CT, and the treatment aims to reduce the symptoms, improve the quality of life, and control the disease. Nevertheless, the prognosis of metastatic esophageal cancer remains poor. The five-year survival rate is 4%, and the median OS is 4-12 months in stage IV esophageal cancer (8). In this study, the median OS is relatively higher than the literature with median 14 months.

Several retrospective and prospective studies have suggested that RT could improve survival in metastatic esophageal cancer (9-11). In a large observational study, 12,683 newly diagnosed metastatic esophageal cancer patients were evaluated according to the treatment type that they received. Compared with CT alone, definitive dose RT was associated with improved survival (8.3 vs. 11.3 months, p=0.001) (9). CT plus palliative dose RT was associated with slightly inferior outcomes (8.3 vs. 7.5 months, p=0.001). They suggest that definitive dose RT may play a role in selected patients whose survival is threatened by local diseases such as airway invading, luminal obstructing tumors. In that study, just 24% of the tumors had an SCC histopathologic subtype contrary to our study, in which 87% of the tumors had SCC. The radiosensitive biological nature of SCC may influence the oncological results like our study in which OS was 24 months with definitive dose RT combined with CT.

In a study 5.970 metastatic esophagus cancer patients from the SEER database evaluated with propensity score analysis (11). RT significantly improved the OS in metastatic SCC of esophageal

cancer especially in younger age [hazard ratio (HR): 0.82; 95% confidence interval (CI): 0.68-0.99], white race (HR: 0.87; 95% CI: 0.76-0.99) and with CT (HR: 0.86; 95% CI: 0.75-0.98) but not in adenocarcinoma histology (median OS for RT group vs. no-RT group- 8.0, 7.6-8.4 vs. 9.0, 8.5-9.5, p=0.073).

In a phase II randomized trial, 60 patients with stage IV SCC esophageal cancer were randomly assigned to CT alone, and concurrent CT with RT. Concurrent chemoradiation was well tolerated and associated with more prolonged progression-free survival (12). The possible mechanism for the role of primary tumoral RT in metastatic disease is unknown. The historical role of RT is to control the local disease with maximal tumoral cell damage. However, RT also has immune-modulatory effects on unirradiated tumoral areas. There is an ongoing study investigating the anti-tumor T-cell response and abscopal effect of palliative RT combined with pembrolizumab in metastatic esophagus, stomach, or gastroesophageal junction cancer patients. They aimed to lead to an increase in tumor-infiltrating cytotoxic T-cells, circulating cytotoxic T-cells, and a reduction in immunosuppressive regulatory T-cells and myeloid-derived suppressor cells in metastatic sites.

Dysphagia, which was not subject to this study, is a common cause of morbidity and requires palliation in metastatic esophageal cancer. The best method for palliation of dysphagia has not been established. RT provides a long-term relief of dysphagia in many retrospective and prospective trials (13-15). A combination CT with RT improves symptoms of dysphagia and has a positive impact on survival in advanced and metastatic esophageal cancer with acceptable toxicity (16,17).

Study Limitations

The primary limitation of the study is the retrospective nature and the small sample size. Selection bias may favor patients who had more aggressive treatment. Disease and treatment-related heterogeneity may influence the results. The metastatic burden of the tumor, which may have an impact on oncological outcomes, is also not evaluated in this study. The majority of people in this series were SCC so the applicability to adenocarcinoma patients are limited. The addition of RT to metastatic sites is a different issue and may influence the results.

CONCLUSION

In patients with metastatic esophageal cancer, 45 Gy and higher dose RT with concurrent CT may contribute to OS in the selected patients after standard treatment. Extensive prospective studies are needed.

Ethics

Ethics Committee Approval: The present study was approved by the University of Health Sciences Turkey, Erzurum Regional Training and Research Hospital (02.12.2019, 2019/15-136).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.T., M.K., O.Ö., H.B., K.A.A.K., Concept: M.T., M.K., Design: M.T., M.K., Data Collection or Processing: M.T., M.K., O.Ö., H.B., K.A.A.K., Analysis or Interpretation: M.T., M.K., Literature Search: M.T., M.K., Writing: M.T., M.K., O.Ö., H.B., K.A.A.K.

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ORIGINAL ARTICLE

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Maculopapular Drug Eruptions: Diversity of Histopathological Changes

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Abstract

Objective: Cutaneous adverse drug reactions are commonly seen in dermatology outpatient clinics thereby comprising a large part of the pathology materials. However, the lack of information about drug usage may cause misdiagnosis. The aim of this study was to discuss criteria that may help in recognition of drug eruptions due to histological patterns.

Methods: Ninety-two patients who were diagnosed with maculopapular rash between 2015 and 2018 at the pathology and dermatology departments of our hospital were examined according to distribution of histopathological changes and patterns.

Results: This study was conducted to evaluate histopathological spectrum of eruption which were known to be drug related that cleared following cessation clinically. Hyperkeratosis or parakeratosis was detected in 26.1% (24/92) and 35.9% (33/92) of all cases, respectively. The most common feature in the epidermis was acanthosis in 88 of 92 biopsies (96%) and the least common feature was atrophy in 4 of 92 biopsies (4%). Dermal inflammation was in 89 of 92 cases (97%). Inflammation was mostly consisted of mononuclear cells. Vacuolar interface dermatitis pattern, spongiotic dermatitis pattern, lichenoid dermatitis pattern, or leukocytoclastic vasculitis pattern was detected in 93.5% (86/92); 58.7% (54/92); 16.3% (15/92); 7.6% (7/92) of all cases, respectively.

Conclusion: Accurate diagnoses of drug eruption are important because they may cause patients' annoyance, hospitalization, economic load, and sometimes be fatal. Like Ackerman emphasized drugs elicit diversity of histological changes but none of the reaction pattern are specific.

Keywords: Maculopapular drug eruption, histopathological reaction patterns, cutaneous drug reactions

INTRODUCTION

Cutaneous maculopapular drug reactions (CDR) are commonly seen in dermatology outpatient clinics associated with the usage of a variety of drugs during daily life (1). The clinical spectrum of CDR is broad. Common CDR symptoms are maculopapular rash, urticaria, fixed drug eruption, angioedema, and contact dermatitis. The majority of CDR is a mild self-limited disease. Few such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia are severe and potentially fatal (1).

Like clinical manifestation, histopathology of drug eruptions also presents in a wide range. Biopsies can show a variety of inflammatory disease patterns and panniculitis-like changes (2). Ackerman emphasized that drugs can elicit any of the nine basic patterns of inflammatory diseases in the skin, and none of those patterns is specific for a drug eruption (2,3). Therefore diversity of CDRs is an important aspect in both dermatology and pathology clinics. Even though drug eruptions are commonly biopsied, histopathological changes are vague. In the literature, some authors declared that histopathological changes in drug

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eruption are non-specific (3) and some said that histopathological diagnosis can be made only with clinical information (4).

In the following, histopathological findings in 92 cases of maculopapular eruption with proven drug-related (with the resolution of eruption following cessation of the drug) were evaluated. We would like to discuss criteria that may aid the diagnosis of drug eruptions due to histological patterns and hypothesize that the coexistence of dermatosis patterns can be a diagnostic clue. We also conclude that lymphatic dilatation in the upper dermis is a common finding of drug eruptions.

METHODS

Ninety-two patients with maculopapular rash who were diagnosed as drug-related between 2015 and 2018 at the department of pathology were studied. The diagnoses were based on morphology in hematoxylin and eosin (H&E) stained sections and confirmed by the clinic. Clinical information was gathered by using the institutes' database records.

The median age of the patients was 50.58±17.70 years. There were 40 men (43.5%) and 52 women (56.5%). All specimens were punch biopsies. H&E-stained slides were reviewed by two pathologists (GK and ÖY).

Statistical Analysis

For statistical analysis, the NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used. Pearson chi-square test and Fisher's Exact test were used to compare descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) as well as qualitative data. Significance was evaluated at $p<0.05$ levels.

Appropriate research ethics and review board permissions were obtained from the Okmeydanı Training and Research Hospital Institute with the reference number 1291 on 05/14/2019.

RESULTS

Ninety-two cases were evaluated. Hyperkeratosis or parakeratosis was detected in 26.1% (24/92) and 35.9% (33/92) of all cases, respectively (Table 1). The most common feature in the epidermis was acanthosis in 88 of 92 biopsies (96%) and the least seen feature was atrophy in 4 of 92 biopsies (4%) (Table 1). Sixteen cases showed sawtooth acanthosis and 3 cases showed psoriasiform acanthosis. Dermal inflammation was in 89 of 92 cases (97%). Regarding the inflammation, localization was superficial in 88% (81/92) of cases and; was both superficial and deep in 8.7% (8/92) of cases (Figure 1A). No inflammation was observed in 3 cases (3.3%) (Table 1). Inflammation mostly consisted of mononuclear cells, and atypical lymphocytes were not observed, as mentioned in some studies (5). Eosinophils and neutrophils were present in 95.7% and 21.7% of all cases, respectively (Table 1).

Necrotic keratinocytes were detected (both encountered at dermo-epidermal junction and scattered within epidermis) in 48.9% (45/92) of all cases (Table 1). The rates of melanophages, basal hyperpigmentation, erythrocyte extravasation or scale crusts were 10.9% (10/92) and 18.5% (17/92), 33.7% (31/92), 7.6% (7/92) respectively (Table 1).

Lymphatic vessels of the superficial dermis were frequently dilated and lymphatic dilatation was present in 93.5% of cases (Table 1).

The incidence for vacuolar interface dermatitis pattern (VIDP) was 93.5% (86/92), the incidence for spongiotic dermatitis pattern (SDP) was 58.7% (54/92), the incidence for lichenoid dermatitis pattern (LDP) was 16.3% (15/92), and the incidence for leukocytoclastic vasculitis pattern (LCVP), was 7.6% (7/92) (Figure 1B).

We examined the dermatitis patterns due to histopathologic features. The correlation between LDP and melanophages was statistically significant ($p=0.009$; $p<0,01$). The correlation between SDP and basal hyperpigmentation was statistically significant ($p=0.030$; $p<0.05$).

Table 1. Histopathologic changes observed in biopsies

Hyperkeratosis		24 (26.1%)
Parakeratosis		33 (35.9%)
Epidermal changes	Acanthosis Atrophy Psoriasiform acanthosis Sawtooth acanthosis	70 (76.1%) 4 (4.3%) 3 (3.3%) 15 (16.3%)
Inflammation	Absent Superficial Superficial + deep	3 (3.3%) 81 (88.0%) 8 (8.7%)
Eosinophils		88 (95.7%)
Neutrophils		20 (21.7%)
Necrotic keratinocytes		45 (48.9%)
Lymphatic dilatation		86 (93.5%)
Pustule formation		12 (13.0%)
Erythrocyte extravasation		31 (33.7%)
Melanophages		10 (10.9%)
Basal hyperpigmentation		17 (18.5%)
Crust formation		7 (7.6%)
Edema of papillary dermis		9 (9.8%)
Elongation of rete ridges		5 (5.4%)

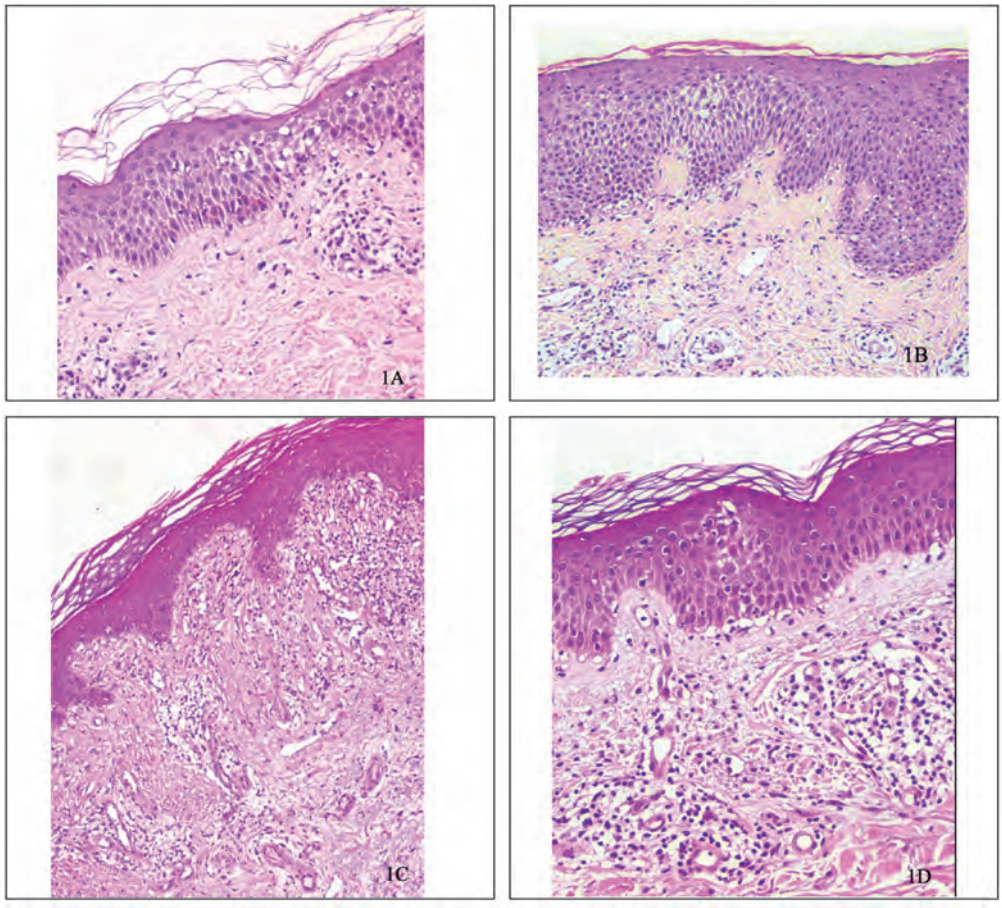

Figure 1. Photomicrographs of selected cases. (A) Basal hyperpigmentation, basket weave hyperkeratosis, spongiosis and vacuolar changes at the dermo-epidermal junction and superficial perivascular inflammation (H&E, x100). (B) Coexistence of VIDP with SDP (H&E, x200). (C) Coexistence of VIDP with LDP (H&E, x100). (D) Combination of VIDP with LCVP and SDP (H&E, x200)

VIDP: Vacuolar interface dermatitis pattern, H&E: Hematoxylin and eosin, LDP: Lichenoid dermatitis pattern, SDP: Spongiotic dermatitis pattern, LCVP: Leukocytoclastic vasculitis pattern

The correlations between VIDP and basal hyperpigmentation, erythrocyte extravasation, melanophages, and lymphatic dilatation were statistically insignificant (p=0.074, p=0.401, p=0.509, p=0.448 respectively). The correlations between SDP and erythrocyte extravasation, melanophages, and lymphatic dilatation were statistically insignificant (p=0.088, p=0.086, p=0.168 respectively).

The correlations between LDP and basal hyperpigmentation, eritrocyte extravasation, and lymphatic dilatation were statistically insignificant (p=0.288, p=0.237, p=0.068, p=0.584, respectively). The correlations between LCVP and basal hyperpigmentation, melanophages, eritrocyte extravasation, and lymphatic dilatation were statistically insignificant (p=0.088, p=0.924 p=0.416, p=0.529, respectively).

Furthermore, coexisting histopathological patterns were examined. Of all cases, one pattern was observed in 29.3% (27/92). Coexistence of two patterns were seen in 62% (57/92) and coexistence of three patterns were seen in 7.6% (7/92) of all drug eruption cases. Regarding the coexistence of patterns, the most common was VIDP with SDP in 55.4% (51/92) (Figure 1B) and VIDP with LDP in 15.2% (14/92) (Figure 1C) of all cases (Table 2).

Table 2. Co-existence of patterns	
VIDP with SDP	51 (55.4%)
VIDP with LDP	14 (15.2%)
VIDP with LCVP	5 (5.4%)
SDP with LDP	5 (5.4%)
SDP with LCVP	3 (3.3%)
VIDP with SDP and LDP	5 (5.4%)
VIDP with SDP and LCVP	2 (2.2%)

VIDP: Vacuolar interface dermatitis pattern, LDP: Lichenoid dermatitis pattern, SDP: Spongiotic dermatitis pattern, LCVP: Leukocytoclastic vasculitis pattern

DISCUSSION

Drug eruptions are the most common disorder of the skin with many morphological features and diagnostic challenges that can resemble other dermatoses. It is crucial to differentiate inflammatory dermatoses from dermatoses like drug eruptions.

Recently it has been stated that a combination of different histopathological patterns indicates a diagnostic clue to drug eruptions (2,6). With this knowledge we would like to evaluate and classify our cases according to their inflammatory reaction patterns, as well as to identify common and overlapping patterns and other accompanying features. Similar to the literature, the most common pattern was VIDP, followed by SDP in our study (2,7,8). Eighty-six of 92 (93.5%) cases showed VIDP pattern as in the study by Naim et al. (7).

To our knowledge, this is the first study submitting data on the coexistence of histological patterns. Our study demonstrated the combination of two or more patterns in 64 of 92 cases (69.5%). Regarding the coexistence of 2 patterns, the most common was VIDP with SDP in 55.4% (51/92) of all cases and the least was SDP with LCVP in 3.3% (3/92). Three of all cases showed a combination of patterns of VIDP, SDP with LCVP (Figure 1D). Psoriasiform or granulomatous patterns are rare forms of drug-related eruptions (6). There were none of these patterns in our cases.

Inflammation is a consistent finding of maculopapular drug eruptions (6,7). According to Naim et al. (7) all cases in their study presented with the inflammatory cells in the dermis. In our study, 3.3% (3/92) of cases were not associated with inflammation (7). Therefore, inflammation is not an indispensable finding for a drug reaction. Our study demonstrated that superficial and deep localized inflammation (8.7%) was lower than the literature (7). Scale crusts were encountered in 7.6% (7/92) of biopsies, unlike the Naim et al. (7) study.

Justiniano et al. (6) stated that the presence of eosinophils is a diagnostic clue. The absence of eosinophils does not rule out drug-related eruptions (6) but drug-related eruptions are often associated with an infiltrate of eosinophils and/or neutrophils (2,8). In our study, eosinophils were present in 88 of 92 cases (95.7%), and neutrophils were present in 20 of 92 cases (21.7%). Naim et al. (7) found eosinophils to be absent in some cases and lower eosinophil counts were detected by other researchers (2,8). Inflammatory infiltrate in dermatoses can also contain eosinophils, therefore accompanying neutrophils to the inflammation can be used as a diagnostic clue.

Melanin incontinence is the result of basal cell damage and observed more frequently in drug or solar damage induced dermatoses (9). Our study showed that the correlation between LDP and melanophages and the correlation between SDP and basal hyperpigmentation was statistically significant. The correlation between LDP with melanophages and the correlation between SDP with basal hyperpigmentation was statistically significant. Therefore, this knowledge can be used when evaluating biopsies taken for drug-related rash.

Naim et al. (7) stated that none of the biopsies showed LCVP contrary to our findings. In our study, 93.5% of biopsy specimens showed lymphatic dilatation in the upper dermis. This was also a common finding in the study by Naim et al. (7).

Similar to the literature, acanthosis was a common finding. In especially irregular acanthosis can be due to some drugs (10).

As a result, we share the same opinion with Weyers and Metze (2), that histopathological diagnosis of drug eruptions can be difficult without clinicopathologic correlation.

CONCLUSION

Drug eruptions are the most common disorder of the skin with many morphological features and diagnostic challenges that can resemble other dermatoses. Histopathological diagnosis of drug eruptions can be difficult without clinicopathologic correlation. However, the coexistence of more than one pattern and lymphatic dilatation can be a diagnostic clue.

Ethics

Ethics Committee Approval: Appropriate research ethics and review board permissions were obtained from the Okmeydanı Training and Research Hospital Institute with the reference number 1291 on 05/14/2019.

Informed Consent: This research project involved the retrospective analysis of archived material (slides) for the purpose of an observational study. No interventional procedures were conducted, and the identities of the patients were protected throughout the study. As a result of the retrospective nature of the study and the use of archive slides with no impact on treatment, informed patient consent was not obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.K., Design: G.K., Ö.Y., Z.B.E., D.K.A., İ.O.T., Data Collection or Processing: Z.B.E., D.K.A., Analysis or Interpretation: G.K., Literature Search: G.K., Z.B.E., Writing: G.K., Z.B.E.

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ORIGINAL ARTICLE

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Frequency of Incidental Prostate Adenocarcinoma Detection in Patients with Radical Cystoprostatectomy for Bladder Urothelial Cancer and Research into the Need for PSA Monitoring for Local-systemic Recurrence

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Abstract

Objective: The incidental prostat adenocancer (PCa) detection rate in pathology material from radical cystoprostatectomy (RCP) has rates varying from 10% to 70% in the literature. Studies have blamed one of the causes for these different rates on the use of cross-section intervals with different widths during the investigation of prostate specimens. In this study was to research the incidental PCa frequency in patients undergoing operation and simultaneously to research the need for PSA follow-up in terms of local-systemic recurrence.

Methods: The pathologies of 115 patients undergoing RCP due to bladder cancer 2011 to 2017 were retrospectively investigated. A total of 26 patients,10 patients with pathology reported as non-urothelial cancer, 5 patients who were female and 11 patients who did not attend follow-up, were excluded. Eighty nine patients were included in the postoperative follow-up. Cystectomy materials were evaluated at 3 mm intervals, and prostate materials at 6 mm intervals. In addition to the evaluation of pathology results, PSA follow-up for at least 6 months was applied to all patients.

Results: In study, mean age calculated as 62.8±0.9 years. Concurrent prostate adenocarcinoma was detected in 18 (20.2%) patients. Preoperative PSA was calculated as 2.06±0.2 ng/mL. PSA follow-up was applied to all patients. PSA elevation was not observed in any patient with benign prostate pathology. PSA elevation was observed in the follow-up of the only patient in the ISUP 3 with PCa. Patients with benign and malignant prostate pathology were compared in terms of age, pre-operative PSA, bladder pathology and survey. No significant difference was found between the groups.

Conclusion: In patients whose prostate pathology was reported as benign, it was observed that there was no increase in PSA even if the cancer was missed. It was thought that these patients with clinically insignificant PCa did not affect the survey in these patients who already had morbidity in terms of bladder tumor.

Keywords: Prostate cancer, bladder cancer, radical cystoprostatectomy, PSA

INTRODUCTION

Prostate cancer (PCa) is in second place for cancer-linked deaths in men after lung cancer (1). The nearly half of PCa patients are asymptomatic. In spite of screening tests, a portion of patients continue their lives without diagnosis and may be diagnosed during postmortem biopsy and autopsy studies after death due to another cause completely (2). The incidental PCa detection rate in pathology material from radical cystoprostatectomy (RCP) operations due to bladder tumors has rates varying from 10% to

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70% in the literature (3,4). Studies have blamed one of the causes for these different rates on the use of cross-section intervals with different widths during investigation of prostate specimens (5). As the section intervals expand, PCa diagnosis may be missed. However, the effect of this missed incidental cancer on patient survival and quality of life is not fully known.

Most prostate pathologies identified by chance are small, localized, well-differentiated clinically insignificant tumors. Only 20% of all PCas is reported to be clinically significant (6).

The primary aim in this study was to research the incidental PCa frequency in patients undergoing RCP operation due to bladder urothelial cancer, and simultaneously to research the need for 3-month PSA follow-up in terms of local-systemic recurrence in the patients with PCa detected and/or not detected; in other words in the probable group with missed cancer diagnosis. The secondary aim was to report opinions about the survival and prognosis of patients.

METHODS

The pathologies of 115 patients undergoing RCP due to bladder cancer in our clinic from January 2011 to January 2017 were retrospectively investigated. A total of 26 patients, 10 patients with pathology reported as non-urothelial cancer, 5 patients who were female, and 11 patients who did not attend follow-up, were excluded from the study. Finally, a total of 89 patients undergoing RCP due to urothelial cancer was included in the postoperative follow-up. None of the patients had previous PCa diagnosis before the operation.

Preoperatively, digital rectal examination findings, PSA values and imaging methods were assessed. No patient had transrectal prostate biopsy performed before RCP. The prostate tissue was investigated at 6 mm section intervals. Patients with identified adenocarcinoma had the remaining prostate tissue included in follow-up and reviewed again. Bladder tumor pathologies were assessed according to TNM classification, while those with simultaneous PCa identified were assessed for volume, surgical margins, TNM classification and Gleason rating system according to ISUP classification.

Patients with postoperative incidental PCa identified were followed up with PSA at 3-month intervals, while other patients were followed at 6-month intervals.

Statistical Analysis

Care was taken to ensure that patients had at least two 6-month PSA checks. While making a descriptive statistical evaluation, categorical percentage (%) and frequency for variables; median minimum- for numeric variables maximum; and mean ± standard deviation values were used. Two variables Correlation analysis was used to determine the relationship between data. Groups with each other chi-square for categorical variables and Mann-Whitney U for numerical variables test was used. The study performed assessments retrospectively. The analysis of data used a statistical analysis program (SPSS, version 20.0). Statistical significance was set as $p<0.05$.

RESULTS

The study included 89 male patients with mean age calculated as 62.8±0.9 years. Patients were followed for mean 22.7 months (6-72). Urinary diversion method were orthotopic ileal pouch for 35 patients (39.3%), non-continent ileal conduit in 36 patients (40.4%) and ureterocutanostomy for 18 patients (20.2%).

When cystectomy specimens are investigated according to TNM classification, 13 patients were pT1 stage (14.6%), 18 patients were pT2 stage (20.2%), 26 patients were pT3 stage (29.2%), 20 patients were pT4 stage (22.5%), 7 patients were pTa stage (7.8%) and 5 patients were pT0 stage (5.6%). The results for cystoprostatectomy specimens identified simultaneous PCa in 18 patients (20.2%). When these 18 patients were investigated, according to ISUP classification, 15 patients were stage 1 (83.3%), 2 patients were stage 2 (11.1%) and 1 patient was stage 3 (5.6%). When all patients were considered, the mean preoperative PSA was calculated as 2.06±0.2 ng/mL (Table 1).

When the preoperative PSA values of incidental PCa patients are investigated, 3 patients were identified to have high PSA values according to age. Biopsy accompanied with transrectal ultrasound was not considered necessary for these patients as it would not change the final treatment decision. When these 18 patients were investigated, according to ISUP classification, 15 patients were stage 1 (83.3%), 2 patients were stage 2 (11.1%) and 1 patient was stage 3 (5.6%) (Table 2).

Patients with simultaneous PCa identified (n=18) and with benign prostate pathology (n=71) were divided into two groups and compared. There was an age difference between the two groups, but statistical significance was not observed (p=0.2). When preoperative PSA values were investigated in both groups, the group with adenocancer detected had values of 2.35 ng/mL, while the other group had values of 1.98 ng/mL. Again, there was a difference but it was not statistically significant (p=0.07). Similarly, group 1 and group 2 had similar features in terms of cystectomy pathologies, postoperative PSA follow-up results, simultaneous prostatic stromal invasion and survival (Table 3).

During 22-month follow-up of all patients, 37 patients died. Of these patients, only 8 had simultaneous PCa. When the causes of death of patients are investigated, none were observed to die due to prostate adenocancer. There was no statistical difference between the two groups in terms of disease-linked survival (56.6-59.2%) (p=0.6).

DISCUSSION

Globally PCa is ranked second among cancers seen in men (7). The incidence is increasing linked to the extension of mean human life expectancy and increased PSA screening. According to autopsy studies, a man of about 50 years of age has 30-50% risk of PCa, while this rate reaches 80% at the age of 80 (2).

Table 1. Patient characteristics (n=89)

Age	62.8±0.9
Preoperative PSA (ng/mL)	2.06±0.2
Incidental PCa	18/89 (20.2%)
Bladder tm. stage	
T0	5 (5.6%)
Ta	7 (7.8%)
T1	13 (14.6%)
T2	18 (20.2%)
T3	26 (29.2%)
T4	20 (22.5%)
PCa stage	
pT2a	12/18 (66.6%)
pT2c	6/18 (34.4%)
PCa ISUP	
STAGE 1 (Gleason 3+3)	15/18 (83.3%)
STAGE 2 (Gleason 3+4)	2/18 (11.1%)
STAGE 3 (Gleason 4+3)	1/18 (5.6%)

PCa: Prostate cancer

Table 2. Characteristics and histopathological findings of patients with prostate cancer detected (n=18)

PSA	Age	Gleason	PCa stage	Bladder tm stage
2.2	66	3+3	pT2a	pT1
3.3	80	3+3	pT2a	pT1
2.8	72	4+3	pT2c	pT4
2.4	77	3+3	pT2a	pT2
3.6	61	3+3	pT2a	pT1
1	60	3+3	pT2a	pT4
4.9	56	3+3	pT2c	pT3
5.9	68	3+4	pT2a	pT4
2	54	3+4	pT2c	pT3
1.6	59	3+3	pT2a	pT2
1.2	59	3+3	pT2a	pT3
1.4	71	3+3	pT2a	pT1
1.5	64	3+3	pT2c	pT4
0.6	49	3+3	pT2a	pT2
1.6	61	3+3	pT2a	pT2
0.5	66	3+3	pT2a	pT1
5.1	63	3+3	pT2c	pT3
2.9	75	3+3	pT2c	pT3

PCa: Prostate cancer

In studies investigating patients undergoing RCP due to invasive bladder cancer, the incidental PCa frequency was identified to be 10 to 70% (8-13). One of the reasons for different rates in these studies is the use of section intervals with different widths during the investigation of prostate specimens (5). Cystoprostatectomy material from 40 cases with prostate tissue sampled at 2-3 mm intervals identified PCa in 45% (14). Another series of 248 cases undergoing RCP found the incidental PCa rate was 4% in tissue samples investigated with sections at 5 mm intervals (15). The data show that as the section intervals grow larger, PCa diagnosis is missed. In our study, specimens were investigated at 6 mm intervals and the incidental PCa rate was found to be 20.2%.

When our study is compared with similar studies in the literature, mean age was younger and simultaneously PCa rates were relatively lower. Second, our clinically significant PCa rate was 16% and this was below the values in the literature (Table 4).

Androulakakis et al. (16) found the presence of PCa and bladder cancer together did not affect the prognosis for both diseases. It appears that patient prognosis is associated separately with the features of each tumor. Pritchett et al. (17) found no difference in terms of survival for patients with both cancers compared to those with only bladder cancer. Poor survival rates in most patients were associated with advanced stage bladder tumor when compared with patients with incidental PCa (18).

In our study, when patients with and without PCa identified are compared, prostate adenocancer did not affect patient survival with 100% cancer specific surveillance. There was no difference survival between the two groups. However, the low number of patients and lack of investigation of disease-specific survival prevent the discussion of this topic. According to these results, PCa accompanying bladder tumor appears not to affect the total survival of patients. The reason for this may be linked to the worse progression of bladder transitional epithelial cell carcinoma compared to PCa. In conclusion, the situation determining surveillance was determined to be the bladder tumor stage.

With the common use of PSA, a significant portion of the increasingly diagnosed PCas are in the clinically insignificant class. Treatment of a disease that will not cause death or other complications will involve unnecessary risks and complications.

The point we wish to draw attention to is that as the group with incidental PCa identified have high rates of clinically insignificant PCa, even if these patients are missed, surveillance

Table 3. Comparison of cases with comorbid prostate cancer (Group 1) and cases with only bladder tumor (Group 2) in cystoprostatectomy samples			
	Group 1 (n=18) %	**Group 2 (n=71) %**	**p value**
Age	65.1±2	62.2±1	0.2
Preop PSA ng/mL	2.35±0.3	1.98±0.2	0.07
Follow-up duration	25±4	22±1	0.9
Bladder tm stage T0 Ta T1 T2 T3 T4	 0 0% 0 0% 5 27.8% 4 22.2% 5 27.8% 4 22.8%	 4 5.6% 8 11.3% 8 11.3% 14 19.7% 21 29.6% 16 22.5%	0.23
Postop PSa mean	0.05	0.02	0.46
Stromal invasion	18/1 (5.6%)	71/14 (19.7%)	0.14
Exitus	8 (44.4%)	29 (40.8%)	0.6
Survival	10 (56.6%)	42 (59.2%)	

Table 4. Some radical cystoprostatectomy series outcomes in the literature						
Study	**Year**	**n**	**Age**	**PCa**	**Significant PCa**	**Section interval**
Pritchet	1988	165	64	45 (27%)	NA	NA
Abbas	1996	40	64	18 (45%)	NA	2-3
Revelo	2004	121	67	50 (41%)	24 (48%)	2-3
Delongchamps	2005	141	62	20 (14%)	14 (70%)	4
Nakagawa	2009	349	65	91 (26%)	68 (74%)	5
Gakis	2010	95	68	26 (27%)	7 (27%)	4-5
Aytac	2011	300	62	60 (20%)	40 (66%)	3-5
Alsinnawi	2012	110	66	35 (32%)	10 (28%)	4
Chang Cho	2013	96	66	39 (40%)	20 (51%)	4
Türk	2015	126	66	26 (20%)	8 (30%)	3
Fragkoulis	2016	64	69	22 (34%)	6 (27%)	4-5
Heidegger	2017	213	71	113 (50%)	59 (52%)	2-3
Our work	2017	89	62	18 (20%)	3 (16%)	6

will not change much. After all, these patients were operated and PCa that may emerge in the future was detected and treated while localized. Even if local or systemic recurrence foci are identified in these patients, it is considered to be low-grade PCa and surveillance will not change.

Study Limitations

Limitations of our study are that it was retrospective, had a short follow-up duration and pathologies were not assessed by the same specialist.

CONCLUSION

When literature data is investigated, in addition to differences like race and age, we see section intervals provide different results. When designing our study, we determined that different section intervals provided very different outcomes. Questions were asked whether this difference caused us to miss some cancers and whether these missed cancers were significant for the patient's clinical status and surveillance. In conclusion, it was not considered necessary to perform PSA follow-up in the group with benign incidental prostate pathology and clinically insignificant prostate cancer. It is considered that the surveillance of these patients should be determined by bladder cancer.

Ethics

Ethics Committee Approval: This study involving human participants was in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki

Declaration and its later amendments or comparable ethical standards. Institutional review board of İzmir Katip Çelebi University (date: 09.08.2017, number: 170) approved this study.

Informed Consent: Informed consents were obtained from all research participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.S.D., Y.Y., Y.A., S.Ö., Concept: A.S.D., Y.Y., Y.A., Design: A.S.D., Y.Y., Y.A., Data Collection or Processing: A.S.D., Analysis or Interpretation: A.S.D., O.K., S.Ö., Literature Search: A.S.D., O.K., Writing: A.S.D.

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ORIGINAL ARTICLE

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The Effect of Associate Professorship Criteria on Emergency Medicine Congresses in Turkey

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Abstract

Objective: To evaluate the situation concerning oral and poster presentations given at Turkish and International Scientific Medical Congresses and adding to scientific knowledge before and after the change in associate professorship eligibility criteria that occurred in December 2016.

Methods: Poster and oral presentations at four consecutive emergency medicine congresses held between 2015 and 2018 by the Emergency Medicine Physicians Association of Turkey were included in the study. As data were collected from presentation booklets accessed online, ethics committee approval was not obtained. Since the associate professorship eligibility criteria changed in December 2016, the last two congresses before that date and the following two after they were compared. Numbers of authors, domestic and international participation rates, the departments involved, and the presence or absence of oral or poster presentations were assessed.

Results: Members of emergency medicine departments contributed to congresses with significantly more case reports than other participants ($p<0.001$). Presentations at congresses held before the change in associate professorship criteria in December 2016 involved larger numbers of authors, while those appearing after the change involved fewer names ($p<0.001$). Participation involved more poster presentations before the change in criteria, while the proportion of oral presentations increased after the change ($p<0.001$). Participation in congresses prior to the change in criteria more frequently involved case reports, while the proportion of original articles increased thereafter ($p<0.001$).

Conclusion: Presentations at congresses held prior to the change in associate professorship criteria involved a large number of author names, while fewer author names were observed following the change in criteria. In addition, prior to the change, participation involved more poster presentations, while the proportion of oral presentations increased after that change.

Keywords: Associate professorship criteria, oral presentation, congress, academic advancement

INTRODUCTION

Scientific medical congresses are an important component of ongoing medical education. As in other departments, these are a setting for scientific activity in which academics share their latest studies and unusual cases with colleagues for the advancement of science in the field of emergency medicine. This may take the form of oral or poster presentations once approval has been received from the relevant congress scientific committee. Several factors affect the selection of these presentations by participants (1).

Various factors affect these presentations in different countries. One such factor in Turkey involves the associate professorship eligibility criteria. These criteria in Turkey changed in December 2016. Prior to that date, the criteria did not include oral or poster

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presentations at scientific assemblies (2). Several amendments were made to the eligibility conditions after December 2016. However, in December 2016, a legal amendment imposed a new basic condition of "scientific activity corresponding to a minimum of 100 in the relevant scientific field" on candidate associate professors (3). Among these changes, under item A under the heading of scientific meetings in Article 9, five points are awarded for oral presentations given at international scientific meetings and contributing to the field of science. Under item B, two points are awarded for oral presentations at Turkish scientific meetings and contributions to science, and at least five points must be obtained within the scope of that item. The maximum permitted total is 10, and the score for only one presentation at the same congress can be included. While oral presentations are included in the scoring, poster presentations are not.

The purpose of this study was to evaluate the effect of the new associate professorship eligibility criteria, applicable to all the health sciences, on the participation by emergency medicine specialists in these congresses with oral and poster presentations.

METHODS

Poster and oral presentations at four consecutive emergency medicine congresses held between 2015 and 2018 by the Emergency Medicine Physicians Association of Turkey (ATUDER) were included in the study. The data were collected from the association's presentation booklets available online (4). Since the associate professorship eligibility criteria changed in December 2016, the last two congresses before that date and the following two after it were compared. Numbers of authors, participation from Turkey and overseas, primarily the proportions of the emergency medicine department as well as other departments, and the presence or absence of oral or poster presentations were examined and assessed. Our study is a retrospective observational study. Ethics committee approval is not required as it is obtained from information accessible over the internet.

Statistical Analysis

The study data were loaded onto Statistical Package for the Social Sciences (SPSS) version 15.0 software (SPSS) for analysis. The data were expressed as mean ± standard deviation, mean, and percentage values. The chi-square test was applied in the analysis of categorical variables. P values <0.05 they were compared. Since there was a significant difference between the groups formed by the number of authors in our study, the post-hoc multiple comparison test was used to reveal which groups this difference was between.

RESULTS

A total of 4.346 presentations published in the online proceeding booklet of the national emergency medicine congresses organized by ATUDER between 2015-2018 was examined in our study. Visual poster and oral presentations in these congresses were evaluated before and after this date due to the new associate professorship criteria published in 2016.

Participant numbers and rates for all branches of health sciences at emergency medicine congresses held in 2015-2018, the mean numbers of authors, and numbers and rates of oral and poster presentations before and after the change in associate professor eligibility criteria are evaluated.

When we evaluated according to branches, the highest number of reports were emergency medicine (93%), general surgery (6.5%), radiology (2.9%), internal medicine (2.6%), neurology (2.4%) and biochemistry (2.4%) were sent by their departments. Considering the number of authors in the papers, the average number of authors was found to be 5.1±2 by the emergency medicine clinic. The number of authors of the other clinics are respectively histology (7.6±1.5), medical biology (7), biochemistry (6.9±1.7), hyperbaric (6.7±2.1), radiation oncology (6.5±3.5), biostatistics (6.4±2) pharmacology (6.1±1.7), family medicine (6.1±2.1) and general surgery (5±2.1) (Table 1). The total number of poster presentations was 2.999, and the total number of oral presentations was 1.347. 94.2% of the poster presentations and 90.4% of the oral presentations belonged to the emergency medicine department. When the total reports were evaluated as articles and case reports, it was seen that the case reports were 77.7% and the original article presentations were 22.3%. When these papers belonging to the emergency medicine department were examined, the percentages of original articles and case reports were found to be 87.5% and 94.6%, respectively. When the total number of papers was examined according to the date of change of associate professor criteria, it was seen that there were 2.177 papers before this date and 2.169 papers after this date (Table 1).

Oral and visual poster presentations appeared with more author names before the change in associate professor eligibility criteria, in December 2016, and with fewer author names thereafter (p<0.001). Participation before the change in criteria more commonly involved visual poster presentations, while the number of oral presentations increased thereafter (p<0.001). Case presentations were more common before the criteria changed, while the proportion of original articles increased thereafter (p<0.001). When the number of authors in the papers was compared before and after the criterion change,

Table 1. Participation numbers and rates among all health science branches at congresses held by the Emergency Medicine Physicians Association of Turkey in 2016-2018 and evaluation of the presantations

	Total number of publications	Number of authors	Presentation type		Type of oral presentation		Criteria change	
			Poster presentations	Oral presentations	Case report	Original article	Before (2015-2016)	After (2017-2018)
	n (%)	Mean ± SD	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Emergency medicine	4.042 (93)	5.1±2	2.824 (94.2)	1.218 (90.4)	3.193 (94.6)	849 (87.5)	2051 (94.2)	1991 (91.8)
Internal diseases	112 (2.6)	5±2.1	68 (2.3)	44 (3.3)	68 (2)	44 (4.5)	71 (3.3)	41 (1.9)
General surgery	282 (6.5)	5±1.9	194 (6.5)	88 (6.5)	19 (5.7)	88 (9.1)	124 (5.7)	158 (7.3)
Dermatology	9 (0.2)	4±1.5	7 (0.2)	2 (0.1)	7 (0.2)	2 (0.2)	6 (0.3)	3 (0.1)
PRC	20 (0.5)	4.4±2.2	11 (0.4)	9 (0.7)	19 (0.6)	1 (0.1)	15 (0.7)	5 (0.2)
Radiology	125 (2.9)	5±1.9	83 (2.8)	42 (3.1)	99 (2.9)	26 (2.7)	58 (2.7)	67 (3.1)
Eye diseases	22 (0.5)	3.9±2.5	13 (0.4)	9 (0.7)	13 (0.4)	9 (0.9)	12 (0.6)	10 (0.5)
Pediatrics	41 (0.9)	3.9±1.9	25 (0.8)	16 (1.2)	22 (0.7)	19 (2)	19 (0.9)	22 (1)
Family medicine	29 (0.7)	5.2±1.1	23 (0.8)	6 (0.4)	15 (0.4)	14 (1.4)	15 (0.7)	14 (0.6)
PTR	12 (0.3)	5.8±2	8 (0.3)	4 (0.3)	7 (0.2)	(0.5)	3 (0.1)	9 (0.4)
ENT	24 (0.6)	5.6±1.7	18 (0.6)	6 (0.4)	19 (0.6)	5 (0.5)	16 (0.7)	8 (0.4)
Psychiatry	23 (0.5)	4.6±1.9	8 (0.3)	15 (1.1)	7 (0.2)	16 (1.6)	15 (0.7)	8 (0.4)
Infectious diseases	24 (0.6)	4.8±1.7	20 (0.7)	4 (0.3)	17 (0.5)	7 (0.7)	17 (0.8)	7 (0.3)
Cardiology	73 (1.7)	4.9±2.3	38 (1.3)	35 (2.6)	36 (1.1)	37 (3.8)	43 (2)	30 (1.4)
Neurology	97 (2.2)	4.7±2.2	67 (2.2)	30 (2.2)	77 (2.3)	20 (2.1)	46 (2.1)	51 (2.4)
Chest diseases	46 (1.1)	5.4±1.9	21 (0.7)	25 (1.9)	16 (0.5)	30 (3.1)	27 (1.2)	19 (0.9)
Orthopedics	88 (2)	4.7±2.3	57 (1.9)	31 (2.3)	59 (1.7)	29 (3)	44 (2)	44 (2)
Urology	46 (1.1)	3.8±1.9	16 (0.5)	30 (2.2)	21 (0.6)	25 (2.6)	13 (0.6)	33 (1.5)
Neurosurgery	78 (1.8)	4.3±2.4	51 (1.7)	27 (2)	57 (1.7)	21 (2.2)	23 (1.1)	55 (2.5)
Pediatric surgery	7 (0.2)	3.1±0.7	3 (0.1)	4 (0.3)	6 (0.2)	1 (0.1)	5 (0.2)	2 (0.1)
Thoracic surgery	96 (2.2)	5.1±1.9	56 (1.9)	40 (3)	71 (2.1)	25 (2.6)	39 (1.8)	57 (2.6)
CVS	83 (1.9)	5.2±1.5	66 (2.2)	17 (1.3)	63 (1.9)	20 (2.1)	67 (3.1)	16 (0.7)
Gynecology	15 (0.3)	4.9±2.3	12 (0.4)	3 (0.2)	9 (0.3)	6 (0.6)	9 (0.4)	6 (0.3)
Pathology	49 (1.1)	5.6±2.2	26 (0.9)	23 (1.7)	22 (0.7)	27 (2.8)	12 (0.6)	37 (1.7)
Microbiology	15 (0.3)	4.9±1.5	10 (0.3)	5 (0.4)	6 (0.2)	9 (0.9)	3 (0.1)	12 (0.6)
Biochemistry	105 (2.4)	6.9±1.7	37 (1.2)	68 (5)	28 (0.8)	77 (7.9)	69 (3.2)	36 (1.7)
Public health	13 (0.3)	6.1±2.1	6 (0.2)	7 (0.5)	2 (0.1)	11 (1.1)	7 (0.3)	6 (0.3)
Anesthesia	102 (2.3)	5±1.9	81 (2.7)	21 (1.6)	81 (2.4)	21 (2.2)	55 (2.5)	47 (2.2)
Biostatistics	37 (0.9)	6.4±2	16 (0.5)	21 (1.6)	6 (0.2)	31 (3.2)	21 (1)	16 (0.7)
Histology	21 (0.5)	7.6±1.5	10 (0.3)	11 (0.8)	2 (0.1)	19 (2)	16 (0.7)	5 (0.2)
Emergency medicine	8 (0.2)	4.9±2	2 (0.1)	6 (0.4)	4 (0.1)	4 (0.4)	5 (0.2)	3 (0.1)
Anatomy	26 (0.6)	5.8±2.3	16 (0.5)	10 (0.7)	11 (0.3)	15 (1.5)	19 (0.9)	7 (0.3)
Physiology	10 (0.2)	5.7±2.5	3 (0.1)	7 (0.5)	1 (0)	9 (0.9)	3 (0.1)	7 (0.3)
Nuclear medicine	14 (0.3)	4.9±1.9	11 (0.4)	3 (0.2)	6 (0.2)	8 (0.8)	12 (0.6)	2 (0.1)
Pharmacology	22 (0.5)	6.1±1.7	14 (0.5)	8 (0.6)	3 (0.1)	19 (2)	11 (0.5)	11 (0.5)
Nursing	9 (0.2)	4.6±1.7	4 (0.1)	5 (0.4)	3 (0.1)	6 (0.6)	1 (0)	8 (0.4)
Radiation oncology	2 (0)	6.5±3.5	-	2 (0.1)	-	2 (0.2)	-	2 (0.1)

Table 1. Continued

	Total number of publications	Number of authors	Presentation type		Type of oral presentation		Criteria change	
			Poster presentations	Oral presentations	Case report	Original article	Before (2015-2016)	After (2017-2018)
	n (%)	Mean ± SD	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Genetics	10 (0.2)	4.9±1	2 (0.1)	8 (0.6)	6 (0.2)	4 (0.4)	4 (0.2)	6 (0.3)
Hyperbaric	3 (0.1)	6.7±2.1	1 (0)	2 (0.1)	1 (0)	2 (0.2)	2 (0.1)	1 (0)
Dentistry	1 (0)	1	-	1 (0.1)	1 (0)	-	-	1 (0)
Medical ethics	2 (0)	3.5±2.1	-	2 (0.1)	-	2 (0.2)	2 (0.1)	-
Medical biology	1 (0)	7	-	1 (0.1)	-	1 (0.1)	1 (0)	-
Clinical psychology	1 (0)	4	-	1 (0.1)	-	1 (0.1)	-	1 (0)
Total	4.346	-	2.999	1.347	3.376	970	2.177	2.169
	(100%)		(69%)	(31%)	(77.6%)	(22.4%)	(50.1%)	(49.9%)

*SD: Standard deviation, PRC: Plastic and reconstructive surgery, PTR: Physical therapy and rehabilitation, ENT: Ear, nose, and throat, CVS: Cardiovascular surgery

Table 2. A comparison of oral and poster presentation numbers and rates at emergency medicine congresses before and after the change in associate professor eligibility criteria in December 2016

	Criteria change		Total	p*
	Before (2015-2016)	After (2017-2018)		
	n (%)			
Number of authors				**<0.001**
One	38 (1.7)	137 (6.3)	175 (4)	
2-5	1.165 (53.5)	1.293 (59.6)	2.458 (56.6)	
6-10	954 (43.8)	733 (33.8)	1.687 (38.8)	
>10	20 (0.9)	6 (0.3)	26 (0.6)	
Post-hoc analysis p values	One vs. 2-5			<0.001
	One vs. 6-10			<0.001
	One >10			<0.001
	2-5 vs. 6-10			<0.001
	2-5 vs. >10			0.003
	6-10 vs. >10			0.037
Type of presentation				**<0.001**
Poster	1.722 (79.1)	1.277 (58.9)	2.999 (69)	
Oral	455 (20.9)	892 (41.1)	1.347 (31)	
Case presentation				**<0.001**
Case report	1.726 (79.3)	1.650 (76.1)	3.376 (77.7)	
Original article	451 (20.7)	519 (23.9)	970 (22.3)	
Congress type				0.259
Turkish	2.160 (99.2)	2.158 (99.5)	4.318 (99.4)	
International	17 (0.8)	11 (0.5)	28 (0.6)	

*: Chi-square test

we found that the decrease in the number of authors after the criterion change was significant ($p<0.001$). Participants did not distinguish between domestic and international conferences with the change in eligibility criteria (Table 2).

DISCUSSION

In the present study, before the change in associate professorship eligibility criteria in December 2016, oral and visual presentations involved larger numbers of author names, but the number of names subsequently decreased. Poster presentation rates also diminished after the change in criteria, whereas a marked increase was observed in oral presentations. This can be explained in terms of the change in associate professorship eligibility criteria. Prior to the change in these criteria, there was no requirement for candidates to contribute to congresses with oral presentations (2). A minimum of five points and a maximum of 10 must be earned from oral presentations at congresses. Oral presentations at international scientific congresses counted for 3 points, and those given at Turkish congresses counted for two (3). The score for each oral presentation is divided equally by the number of authors, and the score awarded to each individual varies depending on the number of authors named. One point noted by a number of candidate associate professors is that less valuable oral presentations after the change in criteria attracted higher scores. As determined in the present study, candidates who are considering becoming associate professors consider these congresses, which count as scientific meetings, as an environment for fulfilling the minimum requirement, making no distinction based on their domestic or international character.

Although the academic career path in Turkey is similar in some respects to those in the United States of America (USA), United Kingdom, Netherlands, and Germany, it also differs in some important aspects. The US system predominates in most countries. A young member of teaching staff in the USA sets out with the title of "assistant professor." In order for a member of the teaching staff to secure the title of assistant professor, he must complete a process developed in the light of the particular university's aims and requirements (5).

Universities' development of their own associate professorship processes and their ability to implement them with no outside influence enables them to function autonomously and scientifically in line with their founding purpose, and gives them the flexibility necessary to manage scientific studies in line with the needs of today's rapidly changing world. After working for 6-7 years, and if the individual's publications and teaching performance are adequate, he is promoted to the rank of "associate professor" (6). In Turkey, there is a requirement to fulfill the minimum conditions set out by the "Inter-University Associate Professor Examination Regulations Board", a centrally-administered body, and these minimum conditions are published in each application period.

Intensive participation in congresses emerged in this study. The four Turkish or international emergency medicine congresses analyzed attracted 4.346 presentations, 1.347 of which were oral. The rate of oral presentations approximately doubled in the period after the change in eligibility criteria compared to the previous period. A previous study examining the publication rates of presentation abstracts at emergency medicine congresses held by the European Society for Emergency Medicine in 2011 and 2012, reported that 1.721 presentations were submitted to the two congresses, 462 of which were oral (7). The numbers of both oral and poster presentations per congress were higher in this study. The principal reason for this is the increase in the participation rate among both emergency medicine specialists and from other departments, compared to the previous period, as a result of the change in associate professorship criteria.

In another study, the total number of papers presented at the National Turkish Otorhinolaryngology and Head and Neck Surgery Congresses, three of the most extensive scientific meetings held in 2008, 2009, and 2010, was 1454, while the total number of papers presented to the four consecutive medical congresses evaluated in the present study was 4.346 (8). Another study reported that 538 papers were presented at the 30th Turkish Cardiology Congress, attracting international participation, in 2014 (9). Although emergency medicine was established only as a main department in Turkey in 1993, it has since produced large numbers of specialists and academics. More emergency medicine specialists aiming to become associate professors than those from other departments seek to fulfill the criteria for associate professorship.

Özdemir and Kutsal (10) concluded that the primary reason for participating in scientific research, at 51.2%, was academic advancement. Participants were found to make no distinction between domestic or international congresses following the change in associate professorship eligibility criteria. We attribute this to participant wishing to be appointed associate professors endeavoring to fulfill the minimum criteria as quickly as possible.

Although meeting the associate professorship eligibility criteria and endeavoring to become an associate professor within a short time is the most important factor that encourages academics to publish, it also entails a number of drawbacks. We think that the contribution of oral presentations to the associate professor

score may reduce the interest in scientific articles because it is more points than the pre-2016 criteria and because it is relatively easy to prepare. Tür and Ersin Aksay (11) reported lower total numbers of publications, first-name author publications and first-name research article numbers, international publication production rates, and total research article numbers among emergency medicine specialists in the post-associate professor period compared to the pre-associate professorship period (12).

Study Limitations

The principal limitation of this study is that only four emergency medicine congresses were included.

There were two emergency medicine associations at the time when the congress data we received in our study were available, we evaluated the ATUDER congress proceedings booklets in order not to create bias between the associations and because it is easier to access the congress proceedings booklets over the internet. We think that examining the data of other departments and other associations of emergency medicine in other studies to be conducted will support our study.

CONCLUSION

Based on the results of our study, we can say that with the change in the criteria for associate professor, the total number of authors decreased in the presented papers and the oral presentations increased compared to the poster presentations. The change in the criteria for associate professor in Turkey has led to an increase in participation from other disciplines to emergency medical congresses. In addition, the change of these criteria has increased the number of oral presentations in emergency medicine congresses. The reason for this can be attributed to the scores given to the oral presentations in the criteria. We think that the change of these criteria has contributed to the development of the scientific activities of emergency medicine physicians in the congress.

Ethics

Ethics Committee Approval: Ethics committee approval is not required as it is obtained from information accessible over the internet.

Informed Consent: Not required.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.S.S., Concept: Ö.U., H.T., Design: A.K., H.T., B.S.S., Data Collection or Processing: A.K., S.Y., Analysis or Interpretation: A.K., B.S.S., Literature Search: Ö.U., S.Y., Writing: Ö.U., S.Y.

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ORIGINAL ARTICLE

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Optimized Hybrid Arc for Improved Sparing of Organs at Risk: Balanced Combination of IMRT and VMAT in Prostate Cancer

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Abstract

Objective: In order to seek a lower toxicity risk prediction in patients with prostate cancer, we have evaluated whether prescribing a potential hybrid radiotherapy of intensity-modulated radiotherapy (IMRT) & volumetric modulated arc therapy (VMAT) optimization might increase sparing of organs at risk (OAR) and target dose conformity.

Methods: The cohort for this dosimetric planning study included ten consecutive prostate cancer patients previously treated with double arc VMAT to 78 Gy. New optimized hybrid arc plans for a combination of IMRT (8 step-and-shoot fix fields: 225°, 260°, 295°, 330°, 30°, 65°, 90°, 135°) and VMAT (182°-178° clockwise) besides new IMRT (8 step-and-shoot fix fields: 225°, 260°, 295°, 330°, 30°, 65°, 90°, 135°) plans were generated per patient. Dose volume histogram parameters were compared between treated VMAT, new IMRT and new optimized hybrid arc plans for OAR doses.

Results: The optimized hybrid arc technique revealed significantly lower rectum (p=0.005) and bladder (p= 0.005) doses compared to stand alone VMAT and IMRT.

Conclusion: The optimized hybrid arc technique appears to combine the advantages of IMRT and VMAT to provide a more conformal and homogeneous plan with better OAR sparing in comparison to standalone VMAT or IMRT plans.

Keywords: VMAT, IMRT, hybrid arc, prostate cancer

INTRODUCTION

Prostate cancer is one of the most prevalent malignant diseases among men, where definitive radiotherapy (RT) plays an indispensable role in their current treatment algorithm (1,2). The triumphant introduction of intensity-modulated RT (IMRT) and its arc-based variant volumetric modulated arc therapy (VMAT) afforded more conformal dose distributions in the target volume(s) as opposed to the historic 3-dimensional conformal RT (3D-CRT) (3,4). The vast majority of the accessible treatment planning studies comparing VMAT and IMRT have reported comparable target volume coverage results, to be specific the planning target volume (PTV) (5-7). Nevertheless, the reported outcomes for the PTV dose homogeneity, the conformality of the dose coverage, and particularly the organs at risk (OAR) doses or sparing capacities are contradictory, with certain insightful reports advocating improved conformality as well as homogeneity with VMAT while others fancying the fixed-field IMRT over the VMAT (4-7).

As of late, a further advance forward, the hybrid arc (HA) technique attained soaring research curiosity given its noteworthy potential

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to improve dose conformity with enhanced planner control and OAR sparing capabilities relative to the VMAT and fixed-field IMRT techniques (8,9). In this respect, Robar and Thomas (10) have convincingly demonstrated that dose homogeneity and OAR sparing was altogether more likely with the novel hybrid combination of the dynamic conformal arc technique and five-field IMRT in RT of the prostate cancer patients, which has been later affirmed by Matuszak et al. (8) by generating fusion treatment with the conformal arc and IMRT fields. The newer hybrid RT approach that typically combines the double arc VMAT and IMRT techniques with differing field numbers has exhibited promising dosimetric results in nasopharyngeal and non-small-cell lung cancer investigations (11,12). We have previously documented that optimized HA technique via combining two half-articulated VMAT technique and static IMRT fields in non-small-cell-lung cancer patients (13) reduced the lung V_{5Gy} and V_{10Gy} dose bath percentages of standalone VMAT and was superior to VMAT in terms of total lung low dose volumes, while delivering faster, more conformal, more homogeneous treatment than standalone IMRT. Hence, in the absence of comparable studies, we have evaluated whether prescribing an optimized hybrid RT of IMRT & VMAT might increase sparing of OAR and target dose conformity in patients with prostate cancer in order to seek a lower risk of toxicity prediction.

METHODS

Patients

Our cohort comprised 10 patients with unfavorable intermediate & high-risk prostate adenocarcinoma, staged as stage $T_{2-3}N_0M_0$ with baseline characteristics given in Table 1. All study patients were treated with a double full arc VMAT technique between January 2016 and January 2018, and were selected for this retrospective dosimetric study. All patients were imaged in the supine position using 3-mm scanner computerized tomography (Philips Brilliance Big Bore 16 slice CT; Philips Medical Systems Inc, Cleveland, OH) slice thickness from the umbilicus to the middle of the femoral bone with full bladder in the A-bar and knee-foot stopper immobilization (CIVCO, Kalona, Iowa). Reproducibility in bladder filling at simulation CT and fractions per day was based on our simulation routine of requesting the patient to empty bladder first, drinking 1 L water in an hour (4-6 cups, 1 cup/10 minutes), informing therapists with the first sign of bladder fullness to measure the filling with a bladderscan (Bladder Scan BVI 6400 bladder volume instrument, Verathon Healthcare, USA) to ensure ≥250 mL, finally verifying the volume measured with bladderscan on the simulation CT; similar procedure per daily fractions were performed accompanied by volumetric cone beam CT for reproducibility.

Treatment Planning

All previously treated plans and study IMRT and optimized plans were generated on the Philips Pinnacle treatment planning system (9.0, Philips Medical Systems Inc. Cleveland, OH) which implements the Collapsed Cone Convolution algorithm. The same dose objectives and weightings of the initial VMAT plans were used for all study plans generated.

The study design was approved by the institutional review board before collection of any patient data, and written informed consent was provided by each participant either themselves or legally authorized representatives.

Conventional Planning

All patients had previously treated VMAT plans, to a total dose of 78 Gy in 39 daily fractions, utilized by two full arcs with the same isocenter rotating clockwise and counter-clockwise starting from 182° and 178° with different collimator angles, respectively.

Table 1. Patient's characteristics

Patient	Age	T-stage	PSA (ng/mL)	Gleason score	PTV volume (cc)
1	68	T3b	15	7 (4+3)	132.73
2	84	T2	4.07	7 (4+3)	108.75
3	78	T2b	15.08	7 (4+3)	102.55
4	77	T2c	7.21	7 (4+3)	90
5	71	T2c	0.5	8 (4+4)	121.22
6	68	T3a	3.93	8 (4+4)	103.25
7	73	T2	8.04	7 (3+4)	93.75
8	80	T2c	3.09	9 (4+5)	142.50
9	79	T3b	6.70	7 (3+4)	112.40
10	71	T2b	22.1	9 (4+5)	100.30

T: Tumor stage, PSA: Prostate-specific antigen, PTV: Planning target volume, cc: cm^3

For each study patient, a static gantry step and shoot IMRT plan was created with 8 coplanar fields of 225°, 260°, 295°, 330°, 30°, 65°, 100°, 135° gantry angles and a total of 160 segments (14).

Optimized Hybrid Arc [(oHA): Optimization of IMRT and VMAT Combination]

oHA technique was created by optimizing an 8-field IMRT (225°, 260°, 295°, 330°, 30°, 65°, 100°, 135° gantry angles) and one full arc VMAT combination, as the optimization strategy is shown in Figure 1. Our strategy was based on three steps: First step to generate one full arc VMAT and 8-field IMRT, where dose weight of 50% for VMAT and IMRT was defined as a starter optimization; second step to start optimization with direct machine parameter optimization for IMRT and the Smart Arc optimization for VMAT separately with same normalization volume chosen to achieve the same coverage for both techniques; third step to allow unlimited field weight ratio for Pinnacle treatment planning system to optimize based on our constraints. The final optimized plan was manually decided based on initial goals of target coverage and OAR sparing. Isodose distribution and DVH graphic for each technique on the sample case are shown in Figures 2 and 3.

Dosimetric comparison: For each case, the competing VMAT, IMRT, and HA plans were compared on the basis of several criteria as specified below. For the rectum, DVH points of $D_{15\%}$ (Gy), $D_{25\%}$ (Gy), $D_{35\%}$ (Gy), and $D_{50\%}$ (Gy), as well as the $V_{75\ Gy}$ (%), $V_{70\ Gy}$ (%), $V_{65\ Gy}$ (%), and $V_{60\ Gy}$ (%), were examined. For the bladder, DVH points of $D_{15\%}$ (Gy), $D_{25\%}$ (Gy), $D_{35\%}$ (Gy), and $D_{50\%}$ (Gy), as well as $V_{80\ Gy}$ (%), $V_{75\ Gy}$ (%), $V_{70\ Gy}$ (%), and $V_{65\ Gy}$ (%), were examined. For total bilateral femur heads and penile bulb, the maximum (D_{max}) and mean (D_{mean}) dose values were compared. For target coverage (PTV), maximum dose (D_{max}), mean dose (D_{mean}), conformality index (CI) as recommended by RTOG and homogeneity index (HI) as recommended by ICRU 83 were compared. Low dose to the body, the body $V_{5\ Gy}$ (%) and $V_{10\ Gy}$ (%) was used as a point of comparison. In addition, a monitor unit [(MU): one fraction] comparison was made between each techniques.

Statistical Analysis

The three different techniques were compared using two-tailed pairwise Wilcoxon signed-ranked tests. A value of $p<0.05$ was considered to indicate statistically significant differences (please provide the open form of each abbreviation where it is used, such as, RTOG, ICRU, V_{60}, $D_{\%35,}$ additionally, is it $D_{\%35}$ or $D_{35\%}$, please correct if not right). We have included 10 random cases as the arbitrary minimum number to demonstrate the statistical difference.

RESULTS

Plan Quality

The IMRT, VMAT, and HA treatment plans were generated for each of 10 prostate cancer patients separately. All plans were clinically acceptable with at least 95% of PTV being covered with %95 of the prescribed dose. The typical isodose distributions for each planning strategy and matching DVH findings were as pictured in Figure 3, while the results of the PTV coverage were as tabulated in Table 2. The PTV mean doses (D_{mean}) of the three techniques were statistically almost indistinguishable, whereas both the CI and the HI of the HA plans were significantly superior to both the IMRT and VMAT plans. "The conformity index CI95 was calculated as the ratio of the volume enclosed by the 95% isodose volume to the part of the target volume receiving more

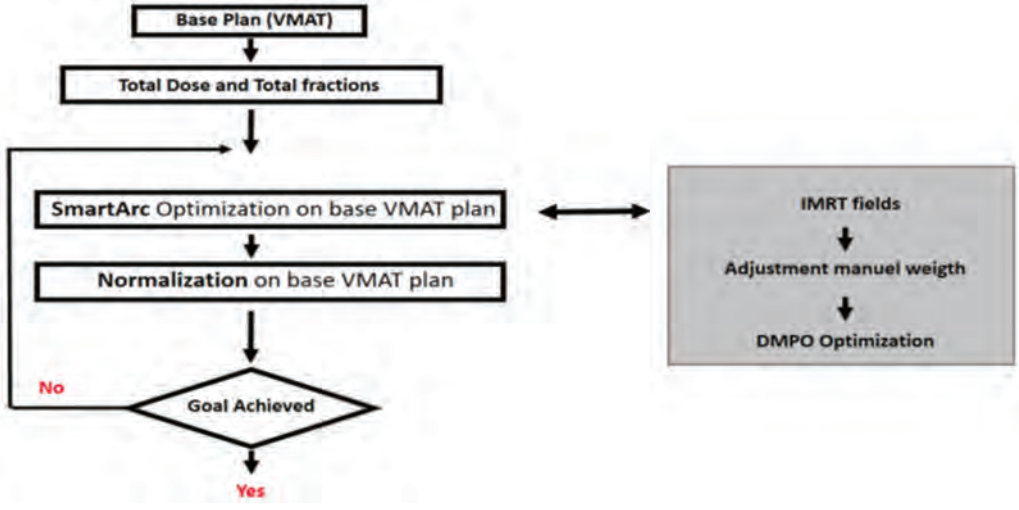

Figure 1. The research strategy for HA optimization

VMAT: Volumetric modulated arc therapy, IMRT: Intensity modulated radiation therapy, DMPO: Direct machine parameter optimization, HA: Hybrid arc

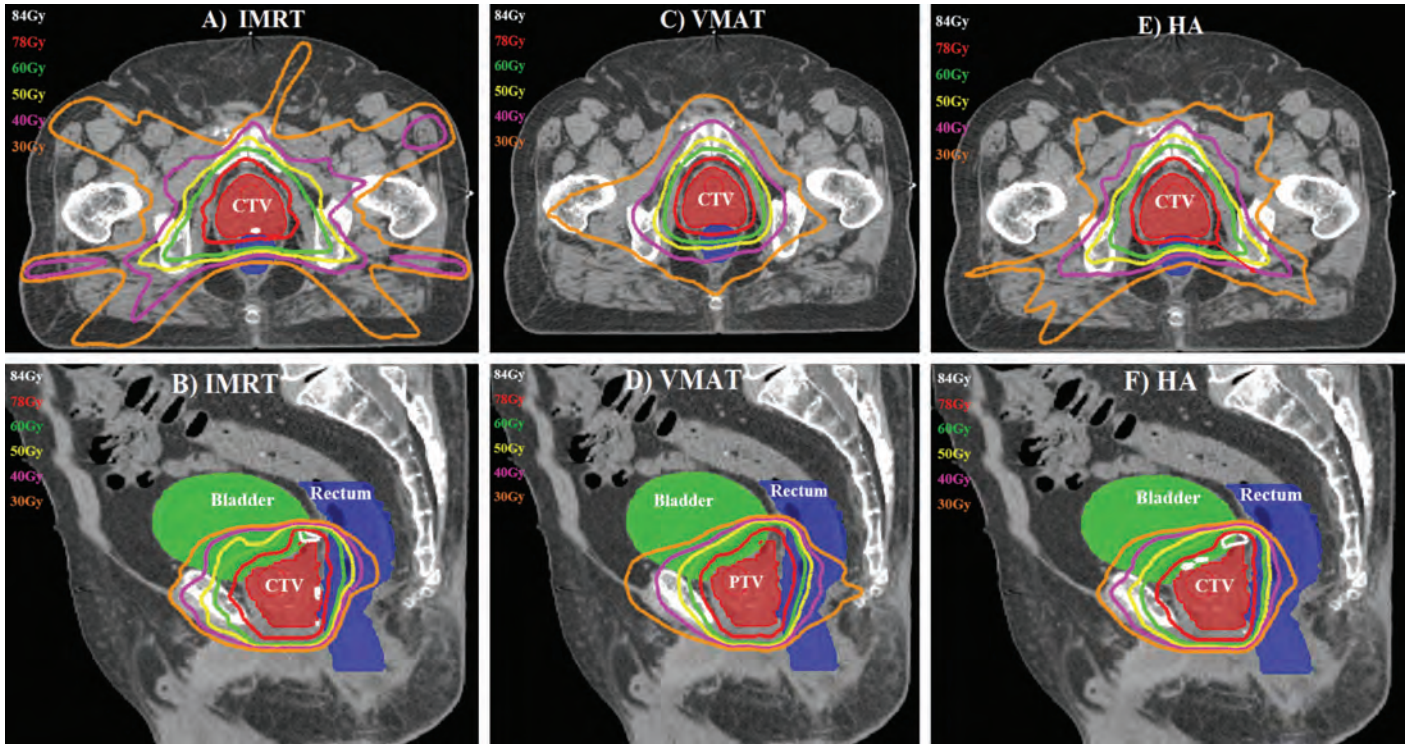

Figure 2. The isodose distribution of A) axial and B) sagittal view of IMRT, C) axial and D) sagittal view of VMAT, E) axial and F) sagittal view of HA
VMAT: Volumetric modulated arc therapy, IMRT: Intensity modulated radiation therapy, HA: Hybrid arc, CTV: Clinical target volume

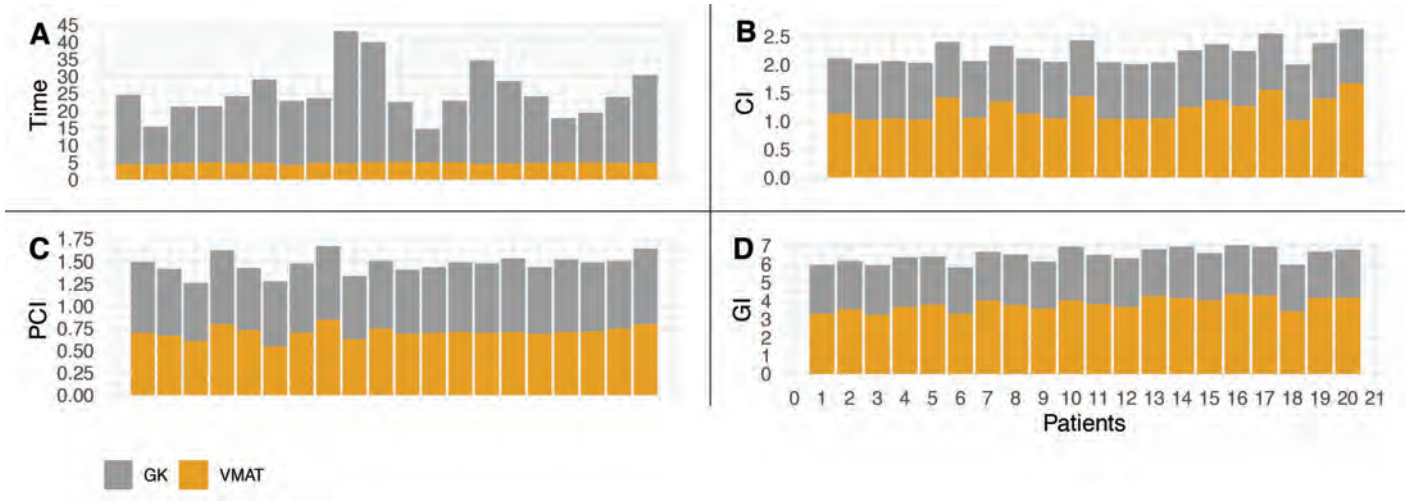

Figure 3. The bar plot of treatment time and index according to GK and VMAT. (a) The treatment times were higher in GK plans (19.00 minutes, range: 9.70-38.50 minutes) compared to VMAT plan (4.80 minutes, range: 4.23-5.15 minutes; $p<0.01$). (b) CI were similar in both treatment plans. (c) and (d) plot showed that PCI and GI indexes for each patient which revealed, GK is higher than VMAT
VMAT: Volumetric modulated arc therapy

than 95% (i.e., CI 95= V95%/TV95%). The 95% isodose was chosen (the ICRU-62 report) to provide 95% target volume coverage. HI was also calculated as HI = D2%-D98%/D 50%, according to the ICRU-83 report.

As presented in Table 2, the MU of VMAT technique was lower than the MUs of IMRT technique (678.7 vs. 814; p=0.028), while, although the MU of the HA was slightly higher than that of the VMAT technique (776.9 vs. 678.7; p=0.037) as expected, yet it was statistically comparable with the calculated MU of the IMRT (776.9 vs. 814; p=>0.05).

Figure 2 exhibits the dose distributions of the three RT techniques in sagittal and axial views. Considering the doses received by the body, either of $V_{5\ Gy}$ and $V_{10\ Gy}$ were lower with the HA technique as opposed to the VMAT (for $V_{5\ Gy}$ 18.8 vs. 22; p=0.008 and for $V_{10\ Gy}$ 14.3 vs. 17.3; p=0.007) and IMRT (for $V_{5\ Gy}$ 19.75 vs. 22; p=0.007 and for $V_{10\ Gy}$ 15.4 vs. 17.3; p=0.014) techniques, respectively. Likewise, the IMRT was found to lead to lower body doses than the VMAT technique.

OAR Doses

The outcomes of OAR doses unveiled from the DVHs of each planning technique are shown in Table 3. Accordingly, the HA technique revealed significantly lower mean OAR values for each organ than the VMAT technique. Likewise, the HA plans were found to provide significantly lower values with the exceptions of the rectal $D_{50\%}$ (Gy) and $V_{65\ Gy}$ (%) as opposed to IMRT plans. The IMRT plans emerged to render meaningfully more acceptable OAR doses in almost all dosimetric parameters, but the rectal $D_{15\%}$ (Gy) and $D_{25\%}$ (Gy) values. Comparably, the HA plans were found to reveal significantly lower OAR doses than the VMAT in all OAR parameters except for the bladder $V_{80\ Gy}$ (%) with a difference of only 0.18%. Moreover, the HA technique was significantly superior over IMRT in provision of lower OAR doses, but bladder except $V_{80\ Gy}$ (%) value. Considering the D_{max} and D_{mean} doses of total femoral heads (left + right) and the penile bulb were significantly lower with the HA planning strategy compared to the VMAT and IMRT strategies.

DISCUSSION

We have demonstrated that our novel oHA plans theoretically revealed significantly lower organ at risk doses for rectum (p=0.005) and bladder (p=0.005) compared to previously treated VMAT and generated IMRT plans.

After almost reaching the technical plateau with either of the IMRT and VMAT, researchers tried to further force the limits by consolidating various advanced RT planning techniques to enable extra technical gains, which may translate to better PTV dose conformality and OAR sparing. Acknowledging these facts, the relatively novel HA technique seems to represent a superior approach in accomplishing preferred treatment designs over the IMRT and VMAT counterparts (8,12,15). Paralleling with the recent hybrid RT literature (11-13), we examined the clinically viable and actually costless blend of VMAT and IMRT to see whether this new technique could meaningfully improve the dose conformity, OAR avoidance, and reduction of the integral dose. Providentially, our results uncovered that the overall plan quality was positively enhanced with the combination of 8-field IMRT and single-arc VMAT techniques, as will be discussed in detail below. Of note, the critical distinction between our current research and the previously published hybrid RT studies is our HA optimization strategy (13), where we consolidated 8-field IMRT and single-arc VMAT techniques explicitly for prostate cancer RT planning.

The VMAT and IMRT techniques have been comparatively studied by various researchers before in terms of dosimetric outcomes of prostate cancer RT planning, however, the results of such studies have for the most part been conflicting (4,5,14,16-20). Some studies have shown that VMAT were all significantly superior to IMRT in most of the relevant values evaluated of target

Table 2. Dosimetric comparison of PTV for IMRT, VMAT and HA plans, including MU, CI HI and body values

Parameter	VMAT	IMRT	HA	p value (VMAT vs. IMRT)	p value (HA vs. VMAT)	p value (HA vs. IMRT)
PTV D_{max} (Gy)	82.77	83.23	82.84	0.005	NS	0.005
PTV D_{mean} (Gy)	79.95	80.27	80.02	0.007	0.047	0.012
MU	678.7	814	776.9	0.028	0.037	NS
CI	1.016	1.009	1.005	0.018	NS	0.014
HI	0.196	0.266	0.208	0.005	NS	0.005
Body $V_{5\ Gy}$ (%)	22	19.75	18.8	0.007	0.008	NS
Body $V_{10\ Gy}$ (%)	17.3	15.40	14.3	0.014	0.007	NS

VMAT: Volumetric modulated arc therapy, IMRT: Intensity modulated radiation therapy, HA: Hybrid arc, PTV: Planning target volume, MU: Monitor unit, CI: Conformity index, HI: Homogeneity index, D_{max}: Maximum dose, D_{mean}: Mean dose, $D_{\%x}$ (Gy): Dose on %X, V_{XGy} (%): Volume on XGy, NS: Not significant

coverage, OARs and normal tissue sparing (4,14,17); on the other hand some studies demonstrate that IMRT is a better technique to spare OARs and has comparable dosimetric parameters of two techniques for plan quality (5,19). Additionally, in a study from MD Anderson Cancer Center, Quan et al. (15) reported that the VMAT was more efficient than the IMRT with regard to the treatment delivery efficiency (14). Nevertheless, whether the VMAT technique may also generate more qualified treatment plan quality than IMRT in the setting of the RT planning of the prostate cancers remains to be clarified. The plan qualities of VMAT and IMRT are for the most part reliant on the notable differences between the number of beam angles and the level of modulation from each angle used (17-21). Results of the joint studies have revealed that larger beam angle numbers with fewer modulations (control points) were significantly more capable of accomplishing superior plan qualities than the philosophy which lean towards many modulations with smaller beam angle numbers (14,15). Comparing VMAT to IMRT plans which ranged from 12 to 24 for the set of patients VMAT plan quality resulted in approximately 30% more monitor units than the 8-beam IMRT plans, as well as similar dose distrubutionas the nember of angle increases (15). On the other hand, particular to the IMRT procedure, larger modulation numbers from many beam angles may still compensate for the insufficient number of beams in the generation of highly qualified treatment plans (14). To minimize unknown certainties, target definitions, pre-set dose constraints, planning strategies, optimization algorithms, and beam angles, all plans were performed and defined by a single physician (US) and physicist (YS). Framing a sound ground for our present 8-field IMRT plan, it has likewise been contended that IMRT with >8 beams was clinically impractical considering its lower conveyance productivity (14).

The overall treatment durations with VMAT plans have been established to be significantly shorter than the IMRT plans

Table 3. Average dosimetric results for OARs sparing for VMAT, IMRT and HA

Parameter	VMAT	IMRT	HA	p value VMAT vs. IMRT	p value HA vs. VMAT	p value HA vs. IMRT
Rectum						
$D_{15\%}$ (Gy)	63.33	61.27	51.95	NS	0.005	0.005
$D_{25\%}$ (Gy)	49.66	47.30	37.56	NS	0.005	0.005
$D_{35\%}$ (Gy)	37.05	33.26	26.63	0.013	0.005	0.005
$D_{50\%}$ (Gy)	22.63	17.28	16.87	0.005	0.005	NS
$V_{75\ Gy}$ (%)	7.09	4.65	3.48	0.007	0.007	0.019
$V_{70\ Gy}$ (%)	11.5	7.42	6.16	0.008	0.008	0.018
$V_{65\ Gy}$ (%)	14.65	8.99	8.85	0.005	0.008	NS
$V_{60\ Gy}$ (%)	17.76	12.16	11.39	0.005	0.005	0.047
Bladder						
$D_{15\%}$ (Gy)	54.14	48.47	47.37	0.005	0.005	0.021
$D_{25\%}$ (Gy)	35.76	29.78	28.97	0.007	0.005	0.013
$D_{35\%}$ (Gy)	24.65	20.11	18.92	0.005	0.005	0.047
$D_{50\%}$ (Gy)	15.34	12.40	11.37	0.005	0.005	0.005
$V_{80\ Gy}$ (%)	1.89	2.11	2.07	NS	NS	NS
$V_{75\ Gy}$ (%)	7.89	6.82	6.07	0.005	0.005	0.012
$V_{70\ Gy}$ (%)	10.13	9.16	7.94	0.032	0.005	0.007
$V_{65\ Gy}$ (%)	11.92	10.69	9.6	0.005	0.005	0.005
Femoral heads						
D_{max} (Gy)	50.19	49.35	45.54	NS	0.028	0.005
D_{mean} (Gy)	22.76	22.10	19.37	NS	NS	0.005
Penile bulb						
D_{max} (Gy)	51.7	53.31	44.71	NS	0.005	0.005
D_{mean} (Gy)	24.58	25.67	22.18	NS	NS	0.037

VMAT: Volumetric modulated arc therapy, IMRT: Intensity modulated radiation therapy, HA: Hybrid arc, PTV: Planning target volume, D_{max}: Maximum dose, D_{mean}: Mean dose, $D_{\%x}$ (Gy): Dose on %X, V_{XGy} (%): Volume on XGy , NS: Not significant

although the total monitor units were comparable (18). Therefore, as can be assumed, treatment durations with HA-IMRT will unavoidably be longer than the VMAT procedures regardless of the primary tumor sites being dealt with. Confirming this reasonable assumption, formerly Zhao et al. (11,12) demonstrated that the hybrid IMRT/VMAT technique was linked with longer treatment durations and higher MUs compared to the VMAT but shorter treatment durations and lower MUs compared to the IMRT. Thusly, our present discoveries concerning the treatment durations and the calculated MUs for HA-IMRT were in accordance with Zhao's findings, albeit neither of the contrasts between HA-IMRT versus VMAT or HA-IMRT versus IMRT could accomplish factual importance. In addition, Quan et al. (15) revealed that hybrid technique having IMRT segment with a different rate between 0% and 100% improved plan quality definitely by the use with 100% IMRT segments (9).

In this current dosimetric research, we mainly attempted to lessen the inevitable disadvantage of the VMAT, mainly the spread out low doses over a large volume of healthy tissue around the PTV by consolidating the VMAT with IMRT: HA-IMRT. We witnessed that the HA-IMRT plans were superior to both of the VMAT and IMRT alone plans concerning more desirable or if nothing else comparative OAR sparing and PTV dose conformity acquired with the HA-IMRT. Moreover, better dose modulation and dose fall-off around the PTV seemed, by all accounts, to be more favorable with HA than the VMAT technique. Our outcomes which recommended lower OAR dosages with HA than both VMAT and IMRT are in acceptable agreement and land further support on the published results of previous research proposing lower OAR doses with hybrid RT technique which incorporated volumetric/conformal arc and IMRT (9,11,12,22). As depicted in Table 2, being in line with the previous hybrid technique studies, the PTV dose homogeneity was also notably improved with the HA technique. In addition, Amaloo et al. (23) have been shown that Hybrid technique included combine of two dynamic IMRT fields with VMAT has a lower dose of integral dose and whole body. However, our HA optimization strategy trying to optimize different treatment techniques together has reduction value in V5 -V10 of the whole body on average compared to VMAT and IMRT. As well as our study improved OAR sparing and target homogeneity, on the other hand, lower receiving 5 Gy and 10 Gy overall. Despite statistical significant results, the differences were small and clinical relevance could be minimal, but in a challenging case, we can propose hybrid planning as a promising technique for OAR preservation.

Our dosimetric study sustains some specific confinements. First, the present research was impeded by its limited sample size as we typically intended to assess our hypothesis in a dosimetric pilot study. Second, we distributed the dose equally (50% for each technique) among the two constituents of our novel technique to carefully adjust the possible advantages and entanglements of the individual procedure. Therefore, various other dose combinations may prompt better PTV and OAR results, particularly for patients presenting with differently sized and shaped prostate glands and overall distinct anatomical variances of the OARs. Third, although HA plans generated here implement an optimal treatment technique for radiation oncology clinics readily treating prostate cancer with IMRT or VMAT techniques without further specific requirements for additional equipment, yet, placing the conduction of further large-scale clinical studies with adequate follow-up times, no clinically pertinent erudition can be got as a result of the examination's dosimetric nature.

CONCLUSION

The results of the present dosimetric study firmly proposed that the novel HA technique described herein was able to consolidate the unique advantages of the IMRT and VMAT techniques in terms of providing more conformal and homogenous dose distributions in the intended targets and lowering the inadvertent dosages got by the OARs, compared with the traditional VMAT technique. The HA technique essentially reduced all bladder and rectum doses except for the $V_{80\,Gy}$(%) of the bladder. Thus, despite recognizing the exact necessity for further studies with sufficient follow-up durations to reliably interpret the likely consequences of such remarkable discoveries on the patients' clinical results, we believe that our current study could be perceived as the first endeavor on a novel but potentially more effective and secure treatment approach for the RT of prostate cancer patients: So-called HA technique, which combines 8-field IMRT and VMAT.

Ethics

Ethics Committee Approval: 2017-111-IRB2.032 approval was obtained from Koç University Faculty of Medicine.

Informed Consent: Written informed consent was provided by each participant either themselves or legally authorized representatives.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.S., Y.B., U.S., Concept: Y.S., Design: Y.S., A.B., Data Collection or Processing: Y.S., Y.B., U.S., Analysis or Interpretation: Y.S., Y.B., A.B., U.S., Literature Search: Y.S., Y.B., A.B., U.S., Writing: Y.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE

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Attitudes Towards the COVID-19 Vaccine: What do Healthcare Professionals Think About the COVID-19 Vaccine?

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Abstract

Objective: This study was conducted to evaluate the thoughts and attitudes of healthcare professionals towards coronavirus disease-2019 (COVID-19) vaccines in the first days of vaccination.

Methods: The study was conducted between January and February 2021 a state hospital. Ethics committee approval and research permission from the Ministry of Health were obtained before starting the study. Participants were asked to fill out the opinion form via Google Forms. The data were evaluated in the SPSS 21 program.

Results: One hundred and sixty of the health workers were women and their mean age was 37.27±9.21 years. Majority of healthcare workers (74.8%) wanted to have any COVID-19 vaccine, and these vaccines were Sinoviac-China (58.7%) Biontech/Pfizer Vaccine-Germany (28.3%), Oxford/Astra Zeneca Vaccine-England, respectively (5.3%), Sputnik Vaccine-Russia (4.0%), and Moderna Vaccine-United States (3.6%). Positive attitude towards the COVID-19 vaccine mean score was 3.56±0.88; the mean score of negative attitude was found to be 3.30±0.70 ($p>0.05$). The mean score of positive attitude towards the COVID-19 vaccine was found to be significantly higher in healthcare professionals with a master's/doctorate education, compared to those with a lower education level.

Conclusion: In our study, it was determined that health workers had positive attitudes towards the COVID-19 vaccine and their negative attitudes were low. The perceptions and attitudes of healthcare professionals, who are at the forefront of the fight against the epidemic, towards COVID-19 vaccines are invaluable both in managing the epidemic and in achieving success in combating the epidemic. Multidisciplinary and multidisciplinary studies are needed to increase COVID-19 vaccination rates.

Keywords: COVID-19 vaccine, idea, attitude, health workers

INTRODUCTION

The new type of coronavirus disease-2019 (COVID-19), which affected the whole world and our country, emerged in the city of Wuhan, China towards the end of 2019 and still continues its effect. To date, more than 396,619.286 cases of COVID-19 have been recorded worldwide, and 5,746.187 deaths have occurred due to this disease (1). There is no officially approved drug for the treatment of the disease. One of the most important components in controlling the COVID-19 pandemic is to provide the highest level of immunity of the population with an effective and safe vaccine (2). With the emergence of COVID-19, vaccine studies have accelerated, and more than a hundred companies or academic institutions around the world are working on COVID-19 vaccines with methods including recombinant vectors, mRNA, DNA, inactivated virus, live attenuated virus, virus-like particles, and protein subunits in lipid nanoparticles (3). Approved COVID-19 vaccines in use;

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RNA-based virus vaccines (Moderna and Pfizer/Biontech) mRNA-1273, inactivated virus vaccine (Sinovac), viral vector vaccine (AstraZeneca/Oxford), ChAdOx1 and BNT162b2 vaccines (4). As of April 21, 2021, there are 14 vaccines approved and started to be used in at least one country (5). The number of individuals vaccinated worldwide is 4.14 billion, and the vaccination rate is 53%. In Turkey, the number of individuals vaccinated is 57.49 million and the vaccination rate is 67.60% (6). Considering the still increasing number of cases and death rates around the world; it can be thought that the vaccination rate is still not at a sufficient level.

Due to occupational risks, healthcare workers are at risk of many infections. Throughout the COVID-19 global pandemic, healthcare professionals at the forefront of combating the epidemic continued to implement high-risk procedures. Protection of healthcare workers from infections plays an important role in controlling hospital-acquired infection transmission (7). One of the most important components in controlling the COVID-19 global epidemic is to ensure the highest level of immunity of the population with an effective and safe vaccine. While immunization has successfully reduced the global burden of disease and death, reliance on vaccines may be affected by several concerns. Despite the COVID-19 pandemic, there is a global distrust of vaccine safety and efficacy (8). Mutations in the COVID-19 virus can increase disease transmission and spread, and reduce the effect of protective antibodies formed by infection and vaccine (9). In addition, the absence of any drug or therapeutic agent clinically approved by the US Food and Drug Administration for the treatment of COVID-19 and mutations in the virus may cause hesitancy to accept the vaccine in individuals (10). It is thought that general vaccine hesitations have an impact on the acceptance of the COVID-19 vaccine. Vaccine hesitancy can lead to delays and vaccine rejection, and even contribute to increased disease transmission (11). Understanding healthcare professionals' hesitations about vaccines can contribute to increased acceptance and rates of COVID-19 vaccines. The aim of this study is to evaluate the thoughts and attitudes of healthcare professionals towards the COVID-19 vaccine in the first days of vaccination.

METHODS

Place and Time of Research

Descriptive cross-sectional this study was conducted at Sakarya Yenikent State Hospital (SYDH) between January 25 and February 8, 2021.

The Universe and Sample of the Research

The population of the study consisted of 507 healthcare professionals working at SYDH between January and February 2021. The sampling method was carried out using the convenience sampling technique. Among the health workers working in SYDH, 254 health workers participated in the study on a voluntary basis, and 254 health workers formed the sample of the study.

Data Collection Tools

Demographic Data and Descriptive Features Form: It consists of 39 questions containing demographic data of healthcare professionals, information on COVID-19 disease and vaccines.

Attitudes Towards COVID-19 Vaccine Scale: This scale, developed by Geniş et al. (12) to assess attitudes towards COVID-19. Vaccine and validated and validated, consists of five Likert-type (1: strongly disagree; 5: strongly agree) and nine items (12). The scale has two sub-dimensions, positive and negative attitudes. Items in the negative attitude sub-dimensions are scored inversely. The total score is obtained by summing the item scores in the scale sub-dimension and the total score is divided by the number of items in that sub-dimension. The higher the score obtained from the positive attitude sub-dimension in the scale, the more positive the attitude towards the vaccine, and the higher the score in the negative attitude sub-dimension, the less negative attitude towards the vaccine. The Cronbach Alpha value of the scale was found to be 0.80 (12,13).

Ethical Approval of Research

The ethics committee of the study was obtained from the Sakarya University Faculty of Medicine Ethics Committee (dated: 15.01.2021 and numbered: E-71522473-050.01.04-595709). In the same period, research permission was obtained from the Ministry of Health Scientific Research Studies.

Data Collection

After obtaining the necessary permissions, healthcare professionals working in SYDH and agreeing to participate in the research were asked to fill out the interview form via google survey. Data collection took approximately eight minutes for each participant.

Statistical Analysis

SPSS 22.0 (Statistical Package for Social Sciences) package program was used for statistical analysis of the data. Display of study data; frequency distribution (number, percentage) for categorical variables and descriptive statistics (mean, standard deviation, median, interquartile range) for numerical variables were given.

The compatibility of the data with the normal distribution was evaluated with the Kolmogorov-Smirnov test ($p>0.05$). Since our data did not show normal distribution, the level of significance between groups was evaluated with Mann-Whitney U test and Kruskal-Wallis test, and One-Way analysis ANOVA was used to examine the difference between categorical variables with more than two groups. Spearman correlation coefficient was used to determine whether there was a relationship between the variables. Cronbach's alpha value was used for scale reliability. Cronbach's alpha coefficient of the Attitudes Towards COVID-19 vaccine scale was 0.881 for positive attitudes; it was determined as 0.762 for negative attitudes. It was seen that the reliability of both attitudes of the scale was high.

RESULTS

One hundred and sixty (63.0%) of the participants were female and their mean age was 37.27±9.21 years. When the distribution of health workers according to their educational status is examined; 9.1% of the healthcare professionals were primary school graduates, 14.2% secondary education, 20.5% associate degree, 37.4% undergraduate, 6.3% postgraduate and 12.6% doctorate graduates. The distribution by profession is; 11.8% were doctors, 42.9% nurses, 2.0% administrators, 11.8% were technicians/technicians, 10.6% were cleaners and 9.8% were from other professions. The mean duration of service was 13.30±8.70 years. 7.9% of the healthcare professionals were in the emergency unit, 1.2% in the operating room, 4.3% in the COVID emergency unit, 13.0% in the COVID service, 7.1% in the COVID intensive care unit, 12.2% in the outpatient clinic, 2.8% were working in the laboratory, 2.4% in the technical service, 11.0% in the inpatient service/clinic, 8.3% in the intensive care unit and 14.2% in other units. While 78.3% of healthcare workers do not have a chronic disease; 21.7% had at least one chronic disease. When the distribution of chronic diseases is examined; of the healthcare workers, 30.9% had hypertension, 20.0% diabetes mellitus, 10.9% allergic asthma, 12.7% heart disease, 12.7% Hashimoto's thyroid, and 12.7% other chronic diseases (these findings are not shown in the table). Demographic characteristics of healthcare workers who want and do not want to be vaccinated and information about COVID-19 are shown in Table 1.

24.4% of healthcare workers reported that they had COVID-19 disease, 35.8% of them had a family history of COVID-19 infection, and 49.6% of them reported that there were people who lost their lives due to COVID-19. 52.4% stated that they received vitamin/mineral/herbal support therapy to prevent COVID-19 disease. While 34.8% of those who took vitamin/drug supplements took vitamin C, 31.6% took vitamin D and 15.9% took zinc; 15.9% were taking herbal tea and 1.8% were taking omega-3 and propolis (these findings are not shown in the table).

78.9% of healthcare workers were exposed to questions about COVID-19 infection and vaccines, and 86.6% thought that there was information pollution about COVID-19 disease and vaccine. While 61.0% of healthcare professionals have confusion about COVID-19 disease and vaccines; 27.6% reported that they believed in conspiracy theories. Again, 52.8% stated that they had the opportunity to look at the results of the COVID-19 vaccine studies; 63.0% found the studies on the vaccine sufficient. More than half of the participants (69.7%) stated that they think the vaccine is effective and they trust the COVID-19 vaccines (64.2%). However, 62.2% reported that they found the information provided about the COVID-19 vaccine insufficient. When the information sources of those included in the research are examined; 27.8% are from the statements of the Ministry of Health, 50.7% are infectious disease specialists/microbiologists, 50.0% are from social media, 41.7% are from television programs/news and 32.6% are from social media (Facebook, Instagram, Twitter, Linkedin etc.) (these findings are not shown in the table).

The majority of healthcare professionals (74.8%) wanted to be vaccinated against any COVID-19 vaccine, and to which COVID-19 vaccine they were asked; Sinoviac-China (58.7%) Biontech/Pfizer Vaccine-Germany (28.3%), Oxford/Astra Zeneca Vaccine-England (5.3%), Sputnik V Vaccine-Russia (4.0%), and Moderna Vaccine-United States (3.6%). He stated that they wanted to be vaccinated. When the factors affecting their vaccination are evaluated; according to the information obtained from television programs, 87.4% of the employees will protect themselves, their families and friends, 89.0% will protect the vaccine community, 88.2% will normalize the people, 54.7% will fulfill the requirements of the institution they work for, 30.3%. According to the information obtained from the internet/social media, 28.3% of them stated that they would be vaccinated because 28.7% wanted their family, 18.9% their friends to be vaccinated, and 16.1% said that they would be vaccinated because there might be a travel restriction for those who are not vaccinated. Despite this, 42.5% stated that they believed in natural and traditional methods of protection from infections and 3.5% stated that they would not be vaccinated due to their religious beliefs; 25.6% stated that they were afraid of vaccines/injections.

When the values of the scales in Table 2 were examined, it was determined that the Cronbach's alpha values were in the range of 0.762-0.881 and the level of reliability was high. In the study, the mean score of the positive attitude towards the COVID-19

Table 1. Demographic characteristics of healthcare workers who want and do not want to be vaccinated against COVID-19 and information about COVID-19 disease and vaccine

		Accepting the COVID-19 vaccine (n=190)	Not accepting the COVID-19 vaccine (n=64)	p value
Age		37.8±9.5 (22.0-60.0) 38.0	37.0±9.1 (20.0-62.0) 38.0	0.577
Gender	Male	77 (40.5)	17 (26.6)	**0.045**
	Female	113 (59.5)	47 (73.4)	
Education status	Primary education	17 (8.9)	6 (9.4)	0.917
	High school	27 (14.2)	9 (14.1)	0.976
	Associate degree	39 (20.5)	13 (20.3)	0.970
	Licence	66 (34.7)	29 (45.3)	0.130
	Degree	13 (6.8)	3 (4.7)	0.539
	Doctorate	28 (14.7)	4)6.3)	0.076
Profession	Doctor	26 (13.7)	4 (6.3)	0.110
	Nurse/midwife	82 (43.2)	27 (42.2)	0.892
	Manager	4 (2.1)	1 (1.6)	0.786
	Technician/technician	23 (12.1)	7 (10.9)	0.802
	Medical secretary	22 (11.6	6 (9.4)	0.626
	Cleaning staff	17 (8.9)	10 (15.6)	0.133
	Other	16 (8.4)	9 (14.1)	0.383
Worked unit	Emergency unit	15 (7.9)	5 (7.8)	0.983
	Operating room	2 (1.1)	1 (1.6)	0.744
	COVID emergency unit	8 (4.2)	3 (4.7)	0.871
	COVID clinic	24 (12.6)	9 (14.1)	0.768
	COVID intensive care unit	11 (5.8)	7 (10.9)	0.165
	Other units	23 (12.1)	13 (20.3)	0.103
	Administrative units	33 (17.4)	7 (10.9)	0.221
	Laboratory	7 (3.7)	0	0.119
	Policlinic	26 (13.7)	5 (7.8)	0.214
	Technical service	6 (3.2)	0	0.150
	Inpatient/clinic	19 (10.0)	9 (14.1)	0.369
	intensive care unit	16 8.4)	5 (7.8)	0.878
Chronic disease presence		43 (22.6)	12 (18.8)	0.514
Information about COVID-19 disease	Having a COVID-19 disease	41 (21.6)	21 (32.8)	0.070
	Presence of people with a family history of COVID-19	68 (35.8)	23 (35.9)	0.982
	Presence of people who lost their lives due to COVID-19 disease in the environment	97 (51.1)	29 (45.3)	0.426
	Taking supplements/vitamins in prevention of COVID-19 disease	100 (52.6)	33 (51.6)	0.882
	Frequent exposure to questions about the COVID-19 illness	152 (80.0)	46 (71.9)	0.175
	Presence of information pollution related to COVID-19	165 (86.8)	55 (85.9)	0.854
	Believing in conspiracy theories about COVID-19	49 (25.8)	21 (32.8)	0.276

Table 1. Continued				
		Accepting the COVID-19 vaccine (n=190)	Not accepting the COVID-19 vaccine (n=64)	p value
Age		37.8±9.5 (22.0-60.0) 38.0	37.0±9.1 (20.0-62.0) 38.0	0.577
Information on the COVID-19 vaccine	Confusion about COVID-19 vaccines	103 (54.2)	52 (81.3)	**0.001**
	I believe in the ethics of the COVID-19 vaccine	167 (87.9)	10 (15.6)	**0.001**
	I trust the COVID-19 vaccine	158 (83.2)	5 (7.8)	**0.001**
	I looked at the COVID-19 vaccine study results	108 (56.3)	26 (42.2)	**0.024**
	I find the COVID-19 vaccine studies sufficient	106 (55.8)	54 (84.4)	**0.001**
	I find the information about the COVID-19 vaccine sufficient	89 (46.8)	7 (10.9)	**0.001**
	I will be vaccinated according to the information I got from the television programs	76 (40.0)	1 (1.6)	**0.001**
	I will be vaccinated according to the information I got from the internet	68 (35.8)	4 (6.3)	**0.001**
	I will be vaccinated because my family wants me to get the COVID-19 vaccine	66 (34.7)	7 (10.9)	**0.001**
	I will be vaccinated because my friends asked me to get the COVID-19 vaccine	43 (22.6)	5 (7.8)	**0.008**
	I will be vaccinated against COVID-19 due to the institution I work for	123 (64.7)	16 (25.0)	**0.001**
	If the COVID-19 vaccine will protect me, my family and my friends, I will get vaccinated	173 (91.1)	49 (76.6)	**0.002**
	If the COVID-19 vaccine will protect the community, I will be vaccinated	175 (92.1)	51 (79.7)	**0.006**
	If the COVID-19 vaccine will normalize the public, I will be vaccinated	173 (91.1)	51 (79.7)	**0.014**
	I'm afraid of vaccines/injections	40 (21.1)	25 (39.1)	**0.004**
	I will not be vaccinated for COVID-19 due to my religious beliefs	6 (3.2)	3 (4.7)	0.566
	I will be vaccinated as there will be a travel restriction for those who are not vaccinated for COVID-19	29 (15.3)	12 (18.8)	0.511

COVID-19: Coronavirus disease-2019

Table 2. Distribution of the mean scores of the sub-dimensions of the attitudes towards COVID-19 vaccine of healthcare professionals

Scales	Number of items	X ± SD	Minimum point	Maximum point	Median	Cronbach's alpha	Varriance
Positive attitude towards COVID-19 vaccine	4	3.56±0.88	1	5	3.75	0.881	12.664
Negative attitude towards COVID-19 vaccine	5	3.30±0.70	1	5	3.40	0.762	12.393

COVID-19: Coronavirus disease-2019, SD: Standard deviation

vaccine of the health workers was calculated as 3.56±0.88 and the mean score of the negative attitude towards the COVID-19 vaccine was calculated as 3.30 ± 0.70 (Table 2).

When the descriptive characteristics of the participants (age, gender, educational status, occupation, unit of work, presence of chronic disease, COVID-19 status etc.) and the attitudes towards COVID-19 vaccine scale score values are compared; there was no statistically significant difference between the mean scores of positive and negative attitudes towards the COVID-19 vaccine according to the variable of having COVID-19 ($p>0.05$) (Table 3). However, the mean score of positive attitude towards

Table 3. Comparison of the score values of the attitudes towards COVID-19 vaccine scale according to the descriptive characteristics of healthcare professionals

	Positive attitude towards COVID-19 vaccine X ± SD/Q_2 (Q_1-Q_3)*	Negative attitude towards COVID-19 vaccine X ± SD/Q_2 (Q_1-Q_3)*
Age		
20-35 years	3.75 (3.00-4.00)	3.40 (3.00-3.80)
36-50 years	3.75 (3.00-4.25)	3.20 (2.80-3.80)
51-65 years	4.00 (3.18-4.56)	3.30 (2.80-4.00)
p	0.267	0.484
Gender		
Male	3.61±0.82	3.25±0.73
Female	3.52±0.92	3.32±0.68
t	0.803	-0.755
p	0.423	0.451
Education status		
Primary education	3.51±1.09	3.03±0.69
High school	3.56±1.07	3.46±0.74
Associate degree	3.51±0.85	3.28±0.73
Licence	3.40±0.81	3.23±0.68
Degree	3.85±0.70	3.48±0.58
Doctorate	3.98±0.73	3.45±0.67
F	2.502	1.723
p	**0.031**	0.130
Profession		
Doctor	3.93±0.72	3.40±0.67
Nurse/midwife	3.50±0.80	3.31±0.65
Manager	3.20±1.19	3.52±0.84
Technician/technician	3.73±0.86	3.40±0.61
Cleaning staff	3.41±1.09	2.95±0.69
Medical secretary	3.56±0.98	3.27±0.85
Other	3.42±0.96	3.40±0.79
F	1.528	1.486
p	0.169	0.184
Worked unit		
COVID emergency unit	3.20±1.02	3.36±0.70
COVID clinic	3.43±0.63	3.12±0.59
COVID intensive care unit	3.52±0.96	3.01±0.60
Emergency unit	3.80±1.08	3.20±1.10
Operating room	3.75±0.75	3.13±0.50
Intensive care unit	3.25±0.81	3.43±0.64
Inpatient/clinic	3.48±0.97	3.07±0.70
Policlinic	3.63±0.83	3.50±0.58
Administrative units	3.73±0.91	3.35±0.71
Laboratory	4.46±0.50	3.48±0.45
Technical service	3.79±0.43	3.76±0.38
Other units	3.43±0.90	3.42±0.68
F	1.581	1.556
p	0.105	0.113
Chronic disease		
Yes	3.59±0.93	3.30±0.74
No	3.55±0.87	3.30±0.69
t	0.305	-0.16
p	0.760	0.987
Contracting a COVID-19 infection		
Yes	3.52±1.00	3.19±0.87
No	3.57±0.85	3.33±0.64
t	-0.435	-1.175
p	0.664	0.243

Table 3. Continued		
	Positive attitude towards COVID-19 vaccine X ± SD/Q_2 (Q_1-Q_3)*	**Negative attitude towards COVID-19 vaccine X ± SD/Q_2 (Q_1-Q_3)***
Family history of COVID-19 infection		
Yes	3.75 (3.00-4.50)	3.20 (2.80)
No	3.75 (3.00-4.00)	3.40 (3.00-3.80)
U	-1.611	-0.893
p	0.107	0.372
Presence of people who have died from COVID-19 in your environment		
Yes	3.75 (3.00-4.06)	3.40 (3.00-3.60)
No	3.75 (3.00-4.00)	3.40 (2.80-3.80)
U	-0.853	-0.133
p	0.394	0.894
Taking vitamin/drug supplements to prevent COVID-19		
Yes	3.75 (3.00-4.12)	3.40 (2.80-3.60)
No	3.75 (3.00-4.00)	3.40 (2.80-3.60)
U	-0.821	-0.844
p	0.412	0.398
Exposure to COVID-19 questions		
Yes	3.75 (3.00-4.00)	3.40 (3.00-3.80)
No	3.75 (3.00-4.00)	3.30 (2.80-3.75)
U	-0.412	-0.920
p	0.681	0.358
Disinformation about COVID-19		
Yes	3.75 (3.00-4.00)	3.40 (3.00-3.80)
No	3.75 (2.93-4.50)	3.10 (2.55-3.80)
U	-0.529	-1.624
p	0.597	0.104
Believing in COVID-19 conspiracy theories		
Yes	3.12±0.85	3.11±0.65
No	3.73±0.84	3.37±0.70
t	-5.116	-2.669
p	**0.001**	**0.008**
State of confusion regarding the COVID-19 vaccine		
Yes	3.25 (3.00-3.75)	3.20 (2.80-3.60)
No	4.00 (3.75-4.75)	3.60 (3.20-4.00)
U	-5.931	-6.305
p	**0.001**	**0.001**
Believing in the effectiveness of the COVID-19 vaccine		
Yes	4.00 (3.50-4.50)	3.60 (3.20-3.80)
No	3.00 (2.50-3.00)	2.80 (2.60-3.20)
U	-9.713	-7.369
p	**0.001**	**0.001**
Confidence status of the COVID-19 vaccine		
Yes	4.00 (3.75-4.50)	3.60 (3.20-4.00)
No	3.00 (2.25-3.25)	3.00 (2.60-3.40)
U	-9.979	-6.812
p	**0.001**	**0.001**

Table 3. Continued		
	Positive attitude towards COVID-19 vaccine X ± SD/Q_2 (Q_1-Q_3)*	**Negative attitude towards COVID-19 vaccine X ± SD/Q_2 (Q_1-Q_3)***
Have you had the opportunity to look at the COVID-19 vaccine study results?		
Yes	3.66±0.992	3.40±0.66
No	3.44±0.83	3.18±0.72
t	2.03	2.558
p	**0.043**	**0.011**
Finding sufficient studies on the COVID-19 vaccine		
Yes	3.50 (3.00-4.00)	3.20 (2.80-3.60)
No	4.00 (3.50-4.50)	3.60 (3.00-3.80)
U	-4.354	-2.899
p	**0.001**	**0.004**
Finding sufficient information about the COVID-19 vaccine		
Yes	4.00 (3.75-4.50)	3.60 (3.20-4.00)
No	3.25 (2.75-3.75)	3.20 (2.80-3.60)
U	-6.363	-3.910
P	**0.001**	**0.001**
Wanting to be vaccinated against COVID-19		
Yes	4.00 (3.50-4.50)	3.40 (3.00-3.80)
No	2.75 (2.00-3.00)	2.80 (2.60-3.20)
U	-10.049	-6.368
p	**0.001**	**0.001**
According to the information I got from the TV, I will be vaccinated		
Yes	3.92±0.78	3.55±0.72
No	3.40±0.88	3.19±0.66
t	4.704	3.834
p	**0.001**	**0.001**
I will be vaccinated according to the information I have obtained from the internet/social media		
Yes	3.86±0.83	3.59±0.69
No	3.44±0.88	3.18±0.67
t	3.430	4.244
p	**0.001**	**0.001**
I will be vaccinated because my parents want me to be vaccinated		
Yes	3.66±0.77	3.31±0.69
No	3.52±0.93	3.29±0.71
t	1.246	0.132
p	0.215	0.895
I'll be vaccinated because my friends want me to be		
Yes	3.67±0.81	3.28±0.78
No	3.53±0.90	3.30±0.68
t	0.941	-216
p	0.347	0.829
I will be vaccinated because the institution I work for wants me to be		
Yes	3.75 (3.25-4.25)	3.40 (3.00-3.80)
No	3.50 (2.75-4.00)	3.20 (2.80-3.60)
U	-2.930	-2.226
p	**0.003**	**0.026**

Table 3. Continued

	Positive attitude towards COVID-19 vaccine X ± SD/Q_2 (Q_1-Q_3)*	Negative attitude towards COVID-19 vaccine X ± SD/Q_2 (Q_1-Q_3)*
If the vaccine will protect me, my family and my friends, I will get vaccinated		
Yes	3.75 (3.00-4.00)	3.40 (3.00-3.80)
No	3.25 (2.00-4.50)	3.50 (2.80-3.60)
U	-1.635	-0.269
p	0.102	0.788
I will be vaccinated if the vaccine will protect society		
Yes	3.75 (3.00-4.00)	3.40 (3.00-3.80)
No	3.00 (2.00-4.00)	3.40 (2.80-3.80)
U	-2.044	-0.167
p	**0.041**	0.867
I will be vaccinated if the vaccine will normalize the people		
Yes	3.60±0.84	3.28±0.70
No	3.24±1.15	3.42±0.67
U	1.667	-1.023
p	0.105	0.307
Fear of injections/vaccinations		
Yes	3.16±0.83	3.13±0.68
No	3.69±0.86	3.36±0.70
t	-4.321	-2.245
p	**0.001**	**0.026**
Believing in traditional solutions		
Yes	3.50 (3.00-4.00)	3.20 (2.80-3.60)
No	3.75 (3.00-4.50)	3.40 (3.00-3.80)
U	-2.524	-1.835
p	**0.012**	0.067
Not wanting to be vaccinated due to religious belief		
Yes	3.00±1.06	2.73±0.80
No	3.58±0.87	3.32±0.69
t	-1.944	-2.498
p	0.053	**0.013**
Requesting vaccination due to travel restriction		
Yes	3.36±0.80	3.12±0.72
No	3.60±0.90	3.33±0.69
t	-1.554	-1.808
p	0.121	0.072

COVID-19: Coronavirus disease-2019, SD: Standard deviation

the COVID-19 vaccine was found to be significantly higher in healthcare workers with a master's/doctorate education compared to those with a lower education level ($p<0.05$).

In the study, those who do not believe in conspiracy theories about COVID-19 compared to those who believe in conspiracy theories; according to those who are not confused about the COVID-19 infection and vaccine, and those who are confused about the subject; according to those who believe in the effectiveness of the COVID-19 vaccine and those who do not believe in the effectiveness of the vaccine; according to those who trust the COVID-19 vaccine and those who do not; according to those who look at the results of the COVID-19 vaccine studies and do not look at the results of the vaccination studies; according to those who do not find the COVID-19 vaccine studies sufficient; according to those who find the information about the COVID-19 vaccine sufficient; according to those who want to be vaccinated against COVID-19 and those who do not want to be vaccinated; according to the information obtained from television, those who want to be vaccinated according to the information obtained from television, according to those who do not want to be vaccinated; according to the information obtained from the internet/social media, those who want to

be vaccinated according to the information obtained from the internet/social media, according to those who do not want to be vaccinated; According to those who want to be vaccinated because the institution they work for wants to be vaccinated, and therefore do not want to be vaccinated; those who were not afraid of injections/vaccines had higher positive and negative attitudes towards the COVID-19 vaccine and were statistically significant ($p<0.05$).

In addition, among the healthcare professionals participating in the research, if the COVID-19 vaccine will protect the society, those who want to be vaccinated compared to those who do not want to be vaccinated; it was determined that those who do not believe in traditional solutions have a higher mean score of positive attitudes towards the COVID-19 vaccine than those who believe in these solutions and are statistically significant ($p<0.05$). Those who did not decide according to their religious beliefs and thought about getting vaccinated had higher negative attitudes towards the COVID-19 vaccine than those who did not think about getting vaccinated because of their religious beliefs, and were evaluated as statistically significant ($p<0.05$).

DISCUSSION

One of the most important components in controlling the COVID-19 epidemic is to provide the highest level of community immunity with an effective and safe vaccine. Vaccination is an extremely safe, effective and inexpensive method for the prevention of infectious diseases (14). The aim of vaccination is to protect human health by preventing severe disease, morbidity and mortality. It has been reported that mortality due to the disease decreased significantly in the country where the disease was detected, with an effective vaccination strategy and sufficient immunity to be achieved (15). It has been reported that the immunization rate among individuals can be between 55% and 82% depending on the COVID-19 prevention and control strategies in a society (16). This rate may vary between regions and even countries depending on the socio-economic situation, regional differences and the sensitivity of the society. In a study conducted with healthcare professionals, it was reported that approximately two-fifths of healthcare professionals (n=92, 39.3%) agreed to receive the COVID-19 vaccine (17). In the study conducted by Roy et al. (18) on healthcare workers, it was reported that only 63% of healthcare workers would be vaccinated against COVID-19. In a study conducted in Iran, it was stated that only 64.3% of the participants agreed to receive any COVID-19 vaccine, and in a study conducted in Kenya, 52.4% of Kenyans were willing to receive a COVID-19 vaccine (19). In our study, according to the literature, it was determined that the participants were more willing (74.8%) to receive any COVID-19 vaccine. It was thought that the high rate in our study was due to the fact that the COVID-19 vaccination program initiated in our country was given priority to the vaccine and that health workers had easy access to the vaccine.

At the beginning of the factors affecting the success of vaccination are individuals' perceptions and trust towards the vaccine. In a study conducted with healthcare professionals in the USA; although it is stated that the vast majority of healthcare workers are willing to be vaccinated in the first wave of the COVID-19 pandemic, it has been reported that one out of every six healthcare workers is reluctant to be vaccinated due to concerns arising from the lack of information about the efficacy and safety of the vaccine. In addition, it was found in the study that healthcare professionals have very strong negative feelings about allergies that may develop after vaccination, indicating their distrust of the vaccine (18). In the study of Agyekum et al. (17); it has been reported that the vast majority of healthcare workers (64.5%) are reluctant to accept COVID-19 vaccines due to their concerns about the safety of vaccines. In our study, it was seen that healthcare professionals trust the COVID-19 vaccines at a rate of 64.2% and this confidence rate is similar to the literature. It was thought that this confidence rate may be due to the high rate of information pollution (86.6%) by healthcare professionals regarding COVID-19 vaccines. We believe that the level of confidence in and acceptance of the vaccine can be increased by identifying the factors that will affect the confidence of healthcare professionals towards the vaccine and developing vaccination strategies for this.

In our study, there was no statistically significant difference between the positive and negative attitude scores of healthcare professionals according to age, gender, occupation, unit of work and chronic disease variables ($p>0.05$); a significant difference was found in the positive attitude score according to the profession variable ($p<0.05$). In the study of Çopur and Karasu (20), there was no significant difference in the positive and negative attitudes of individuals towards the vaccine according to gender ($p>0.05$); it has been reported that there is a significant difference in negative attitude scores according to age and in positive and negative attitude scores according to the presence of chronic disease ($p<0.005$). Elmaoğlu et al. (21), in their study evaluating the relationship between the perception of COVID-19 control in individuals and the attitude towards the COVID-19 vaccine, reported that the positive and negative attitude scores of individuals towards the COVID-19 vaccine were similar according to age (respectively, $p=0.0.450$; $p=0.271$). In a study, when the score ratios of positive-negative attitudes

towards the vaccine were evaluated according to gender, it was reported that there was a significant difference between males and females in the rates of positive attitudes and that males had a more positive attitude towards the vaccine than females (22). In a study evaluating individuals' attitudes towards the COVID-19 vaccine; the positive attitude mean scores of women were significantly higher than men's; it was stated that negative attitude scores were similar according to gender (21). In our study, positive vaccination attitude scores of healthcare professionals with higher education levels were found to be significantly higher. However, negative vaccination attitudes are similar. In the study conducted by Elmaoğlu et al. (21), individuals with high educational status had significantly higher positive attitude scores towards the vaccine; negative attitude scores were reported to be similar. In a study examining the willingness to vaccinate against COVID-19 in China, it was reported that the majority of individuals willing to be vaccinated were university graduates, and there was a statistically significant relationship between education level and willingness to be vaccinated (23). In another study; It has been shown that undergraduate and graduate students are more willing to be vaccinated and there is a significant difference between vaccinated status according to education level (24). The results of our study are similar to the literature; it has been seen that those who want to be vaccinated are in the majority and those with a higher education level are more willing to be vaccinated. It was thought that this result was related to seeing the vaccine as an important factor in protection from the epidemic, that education also increased this awareness, and accordingly, the attitude of health professionals to be vaccinated positively.

In our study, it was observed that the status of having COVID-19 and the scores of positive and negative attitudes towards the vaccine were similar ($p>0.05$). In the study conducted by Yıldız et al. (22), it was reported that there is a significant difference in the positive attitude factor towards the vaccine in case of having COVID-19. In the study, the average of the participants who had COVID-19 was determined as 2.52 and the average of the participants who did not have COVID-19 was determined as 2.06, and it was shown that those who had COVID-19 had a more positive attitude towards the vaccine than those who did not have COVID-19. In the same study, it was reported that there was a significant difference in the mean score of negative attitude towards the vaccine in case of having COVID-19 ($p<0.05$). The average score of the participants who had COVID-19 was 1.64, and the group average of the participants who did not have COVID-19 was 1.81. It is observed that participants who do not have COVID-19 have a more negative attitude towards the vaccine compared to participants who have had COVID-19 (20). In the study of Elmaoğlu et al. (21); it has been reported that the positive and negative attitude scores towards the vaccine are similar according to the COVID-19 positivity in the family of the individuals (respectively, $p=0.282$; $p=0.259$).

In another study evaluating attitudes towards COVID-19 vaccines, it was reported that there was no significant difference in attitudes towards vaccines compared to the statements of the Ministry of Health, which is the most trusted source of information on positive-negative vaccine attitudes, and TV programs, which are the least trusted source ($p>0.05$) (20). In our study, it was determined that there was a significant difference between positive vaccination attitude scores between the information obtained from TV and the variable of wanting to be vaccinated according to the information obtained from the internet/social media ($p>0.05$). According to the information obtained from TV and internet/social media, the positive vaccine attitude scores of health workers who wanted to be vaccinated for COVID-19 were higher. It is thought that healthcare professionals follow up-to-date information about COVID-19 vaccines on TV and internet/social media and accordingly have a positive attitude towards vaccines.

CONCLUSION

In our study, it was concluded that healthcare professionals want to be vaccinated if COVID-19 vaccines will protect themselves, their family, friends and society, they trust COVID-19 vaccines, and healthcare professionals who do not want to be vaccinated against COVID-19 have confusion about COVID-19 vaccines. In addition to the implementation of strict measures in controlling and stopping the COVID-19 pandemic, the most important element is undoubtedly vaccination. Training, symposiums and panels should be organized in order to increase vaccination rates and prevent information pollution and confusion about vaccines, and the information and sharing should be clear, reliable and informative.

Ethics

Ethics Committee Approval: Ethics committee approval of the study was obtained from the Sakarya University Faculty of Medicine Ethics Committee (dated 15.01.2021; E-71522473-050.01.04-595709). In the same period, the Ministry of Health's Scientific Research approval was also obtained.

Informed Consent: Before starting the study, online participation approval was obtained from each healthcare worker.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.K., P.Ö.O., Ş.T., D.A., Design: G.K., P.Ö.O., Ş.T., D.A., Data Collection or Processing: G.K., P.Ö.O., Ş.T., Analysis or Interpretation: G.K., P.Ö.O., Ş.T., D.A., Literature Search: G.K., P.Ö.O., Ş.T., D.A., Writing: G.K., P.Ö.O., Ş.T., D.A.

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ORIGINAL ARTICLE

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The Restrictions and Limitations Exerted During Pandemic Outbreak Did Not Affect the Ratio of the Hip Fractures in the Geriatric Population: A Comparison of the Pre-pandemic Era Versus One Year Amongst the Pandemic Outbreak

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Abstract

Objective: Although the incidence of hip fractures before and during the pandemic is similar, the effect of the epidemic on the distribution of hip fractures and its subtypes cannot be clearly explained. We aimed to elucidate the changes by comparing the number of geriatric hip fractures and the distribution of fracture types between one year of the Coronavirus disease-2019 (COVID-19) pandemic and seven years ago.

Methods: Hip fracture patients over 65 years of age was analyzed retrospectively. The period between March 11, 2020 and March 10, 2021 was called the pandemic period, and the period between March 11, 2013 and March 10, 2020 was called the pre-pandemic period. Mortality rates and fracture morphology were compared between the pre-pandemic period and the pandemic period.

Results: There was no significant difference in the age distribution between pre-covid (80.48±7.38) and Coronavirus period (79.54±7.92) (p=0.163). Likewise, no difference was found between the fracture patterns in both groups (p=0.348). During the pandemic period, femoral neck fractures have become dominant in the younger age group (p=0.038).

Conclusion: Despite the restrictions in the COVID-19 pandemic, geriatric hip fracture rates did not change. At the same time, fracture type distribution was similar to the pre-pandemic period. Pandemic restrictions may have affected hip fracture in the younger age geriatric group. However, this finding alone may not impact the management and planning of geriatric hip fractures during the pandemic.

Keywords: Geriatrics, hip fracture, morbidity, mortality, COVID-19 pandemic, femoral neck fractures

INTRODUCTION

Severe acute respiratory distress syndrome-coronavirus-2 (SARS-CoV-2), also known as 2019 new coronavirus or Coronavirus disease-2019 (COVID-19), first appeared in China on December 31, 2019, and since then, it has spread rapidly and become a pandemic all over the world (1). The effects of this pandemic were widespread, but it had a significant impact on the healthcare system. Due to its effect on healthcare system, the capacity of surgical cases has significantly decreased in orthopedic surgery (1). Although observations show a decrease in the number of emergency department visits and decrease in the number of hip fractures, infact it is mainly resulted from stay-at-home orders, the need for hip fracture care in elderly patients still remains a source of concern (1-3).

Throughout the pandemic, orthopedic trauma services maintained their previous capacity. Patients with hip fractures in the elderly population, in particular, have continued to visit hospitals in numbers comparable to before the pandemic, even in

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areas most affected by the COVID-19 pandemic (3-6). The majority of patients with hip fractures have multiple comorbidities, and they usually developed this fracture after minor falls as a result of poor bone quality and neurologic disorders (3). Even though several studies show that the incidence of hip fractures during the pandemic period shares similar several characteristics with the pre-pandemic period, the effect of the pandemic on fracture type distribution and hip fracture rates is unclear (2,7-12).

The fracture type in geriatric hip fractures may affect the surgical procedure applied, length of postoperative hospitalization, and mortality rate (13-16). Therefore, in terms of managing this patient group in the pandemic period, exact information about fracture distribution can enhance health services. The differences in fracture types and the number of hip fractures studies could be due to two factors: Firstly, restrictions during the pandemic period may change the distribution of fracture types and the number of fractures by causing changes in these patients' activities. Secondly, since most of the studies conducted were small sample studies examining the fracture profile covering short time intervals during the pandemic period, it may have caused differences in fracture types and rates. For this reason, the aim of the study was to clarify this situation by comparing the number of geriatric hip fractures and fracture distribution in one-year period of the COVID pandemic and the 5-year period preceding the pandemic.

METHODS

Study Design and Ethical Consideration

This study was a monocentric, observational, descriptive, and retrospective study. All patients in this study were those who applied to the emergency department of our tertiary hospital or were transferred from outer centers. Approval was received by the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee (number: 191, date: 03.05.2021). Patients with hip fractures were examined between the dates of March 11, 2016, and March 11, 2021. Dates were divided into two groups: The pandemic period, which is the one-year period between March 11, 2020, when the first COVID case was confirmed in Turkey, and March 11, 2021, and the pre-pandemic period, which is the 5-year period before pandemic between March 10, 2016, and March 10, 2020.

Patient Population

All patients over the age of 65 years who applied with hip fractures were involved in the study. The fracture types involved in this study are trochanteric fractures, intracapsular femoral neck fractures, and subtrochanteric fractures (proximal one-third of the femur). Patients with isolated trochanter major fractures, fractures in the middle or distal one-third of the femur, periprostatic femur fractures, and multiple trauma-related fractures were excluded from the study.

Patient Management

The patients were those who had hip fractures that were confirmed radiologically by X-ray in the emergency department or who had been diagnosed with hip fractures in another hospital and were transferred to our hospital's emergency department. Patients were welcomed by the emergency personnel in the beginning and were examined in terms of COVID-19 symptoms. Among the suspicious cases, there were patients with fever or feverless cough or with an illness like influenza. In the first examination, physiological parameters, hematological and biochemical parameters, and thorax computed tomography were all scanned, and polymerase chain reaction (PCR) tests were performed on nasal and throat swabs routinely before the hospitalization. Patients who tested positive or had viral pneumonia findings on computed tomography were referred to an infectious diseases specialist and admitted to the COVID ward. Patients who tested negative were admitted to orthopedics and traumatology ward. In accordance with our hospital's infection control protocols, patients in the orthopedics ward who developed COVID-19 symptoms were isolated and transferred to the COVID ward with the approval of the infectious disease specialist. COVID-19 patients with hip fractures were operated on in a special COVID-19 operating room and received post-operative care in a COVID ward. Patients without COVID were operated on in a "clean" and "non-COVID" operating room and received post-operative care in a "non-COVID" orthopedics ward. Hip fracture operations were accepted as aerosol-forming procedures, and thus fully surgical personal protective equipment was dressed by operating room staff to fully protect both patients and surgeons in both areas.

All operations were performed in the lateral decubitus position. The posterolateral surgical approach was used in patients performed arthroplasty. Osteosynthesis was performed using the proximal femoral nail of Tasarımmed in intertrochanteric and subtrochanteric fractures. The prosthesis from the TST company was used in the hemiarthroplasty procedures.

Data Collection

Codes for International Classification of Diseases-10 (ICD 10), fracture of head and neck of femur, pertrochanteric hip fractures, and subtrochanteric hip fractures (S72.0, S72.1, and

S72.2 respectively) were scanned in the hospital system. After considering the excluded cases, cases involved in the study were classified as pre-pandemic (n=973) and pandemic (n=142) based on the date they applied to emergency department. Patients in the pandemic group were also examined in two subgroups as COVID (+) and COVID (-).

Age, sex, fracture type (intracapsular/extracapsular), length of hospital stays, three-month mortality rates, surgical treatment applied, need for intensive care rates, length of intensive care unit stay, complication rates, and COVID-19 test data were collected.

Categorising stages were completed with three groups; youngest-elderly ones (ranging from ages 65 to 74), middle-elderly group (ranging from ages 75 to 84) and last but not least, the oldest-elderly group (aged 85 years or older) (17).

The first year of the pandemic outbreak was analysed in four quarters (1st quarter: 11.03.2020-10.06.2021, 2nd quarter 11.06.2020-10.09.2021, 3rd quarter 11.09.2020-10.12.2020 and 4th quarter 11.12.2020-10.03.2021).

During the hospitalization period, the time from the first radiological confirmation of the fracture to discharge was calculated (or in case the death, to date of death). A positive COVID-19 situation was defined as the presence of clinical symptoms and a single positive result for the detection of the *SARS-CoV-2 S* gene (*VIASURE SARS-CoV-2* gene real-time PCR detection kit, CerTest Biotect) from nose or throat swab samples or findings compatible with COVID-19 in thorax computed tomography. The COVID-19 situation was considered negative in the absence of clinical symptoms and a negative PCR test.

Statistical Analysis

For quantitative variables, including measures of central tendency, a general descriptive analysis was performed overall and by specific periods. Continuous variables were reported using means and standard deviations if they followed a normal distribution; otherwise, the median and range were used. Absolute frequency and rates were used to summarize categorical variables. Analysis of variance was used to compare continuous variables, and Pearson's chi-squared test was used to compare categorical variables. If a p value was <0.05, it was accepted as statistically significant. IBM SPSS version 25.0 (IBM Corp., Armonk, New York, USA) statistical package was used for all analyses.

RESULTS

Duration of hospitalization period and age-related data are summarized in Table 1. There was no statistically significant difference in both groups according to gender, type of fracture, postoperative intensive care unit care requirement, and complication rates (Table 2). Fracture quantities and fracture patterns were dispersed non-significantly in all four sub-groups (Table 3). There was no statistically significant difference in the age distribution and fracture type distribution between the groups between pre-COVID and COVID periods. The fracture pattern and age distribution of the patients in the pre-pandemic and post-pandemic periods are presented in Table 4. During the pandemic period, femoral neck fractures have become dominant in the younger age group.

DISCUSSION

There was no significant difference in hip fracture patterns and fracture numbers between the pre-pandemic and pandemic periods. Moreover, other crucial data included the femoral neck fractures being the most common fracture pattern among the youngest aged hip fractures. A new strain of COVID was identified as an etiological factor for deadly pneumonia in Wuhan-China, followed by global spread. World Health Organization declared this infection as pandemic on March 11, 2020. At the same time, this is the same date that the first case in Turkey was reported. Due to the lack of preventive inoculation and therapeutic medications, public health precautions such as isolation, social distance, and quarantine were the only options for preventing the disease from spreading (18). Profound changes in social behavior and mobility during the early stages of the COVID-19 pandemic are directly associated with a significant decrease in orthopedics trauma referrals, but fragility fractures remain unaffected and service to these patients should be maintained (10). Furthermore, since these patients are typically elderly, fragile, living in nursing homes, and have multiple comorbidities, they are at a higher risk of developing a serious COVID-19 disease (19). Several cohort studies reported that there are no significant differences in time to operation, type of treatment, complications, or 30-day mortality rates among hip fracture patients admitted during the COVID-19 pandemic compared to those who admitted in the pre-pandemic period (3,5,7,20,21). Our results also support this situation.

Epidemiology is a significant way to predict the resource requirements of health services (10). Considering the burden of the COVID-19 pandemic on the health system, as well as the decisions taken and changes made in the health system, epidemiological evaluations become even more important during this period (18,22). For this reason, numerous studies on geriatric hip fractures in the COVID-19 pandemic have been conducted (1-3,7-9,18-20). Despite the fact that the majority of these studies showed that geriatric hip fractures did not decrease compared to the pre-pandemic period, the results of fracture

Table 1. Age and length of hospitalitaion of the patients included in the study

	Pre-COVID		COVID		p*
	Mean	SD	Mean	SD	
Age (year)	80.48	7.38	79.54	7.92	0.163
Postoperative hospital stay (day)	3.03	3.31	2.57	2.41	0.265
Total hospitalization period (day)	12.49	5.56	11.55	5.41	0.06
Intensive care unit stay period (day)	1.27	1.57	1.38	1.53	0.44

*Student's t-test, COVID: Coronavirus, SD: Standard deviation

Table 2. Dispersion of gender, fracture pattern, the form of surgical treatment, the requirement of ICU, complications and 3-monthly mortality rates amongst groups

	Pre-COVID		COVID		p*
	n	%	n	%	
Gender					
Female	355	36.5	55	38.7	0.604
Male	618	63.5	87	61.3	
Fracture pattern					
Intracapsular	331	34.0	54	38.0	0.348
Extracapsular	642	66.0	88	62.0	
Surgical treatment					
Proximal femoral nail	452	46.5	70	49.3	0.526
Hemiarthrplasty	521	53.5	72	50.7	
Postoperative requirement for ICU					
Present	252	25.9	42	29.6	0.353
None	721	74.1	100	70.4	
Complication					
Present	69	7.1	12	8.5	0.56
None	904	92.9	130	91.5	
90-day mortality					
Present	178	18.3	26	18.3	0.99
None	795	81.7	116	81.7	

*Pearson chi-square test, COVID: Coronavirus, ICU: Intensive care unit

Table 3. Distribution of fracture types and quantities by four divided quarters during the pandemic period

Pandemic periods	Fracture pattern				p*
	Extracapsular		Intracapsular		
	n	%	n	%	
1. Quarter	25	80.6	6	19.4	0.113
2. Quarter	18	54.5	15	45.5	
3. Quarter	21	58.3	15	41.7	
4. Quarter	24	57.1	18	42.5	

*Pearson chi-square test

type distribution differed (2,7-11). According to Malik-Tabassum et al. (7), Arafa et al. (11), and Scott et al. (10), the fracture type distribution was similar to the pre-pandemic period, while in the study of Egol et al. (9), the predominance of femoral neck fractures increased during the pandemic. Slullitel et al. (8) also performed fracture typing using the AO classification and found a statistical difference in fracture type between the pre-COVID and COVID periods. However, neither study discussed the possible reasons for this (8,9). We believe that the source of the difference between these studies is the comparison of patients in the time groups that cover specific months.

Although the general finding in the literature is that the rates of geriatric hip fractures did not change in the pandemic period, there are also opposite results (2,4,7,11,23). While Arafa et al. (11) claimed an increase in hip fracture rates, Nazemi et al. (23) found

Tablo 4. Distribution between the age groups and fracture types of the patients included in the study						
		Fracture pattern				
		Extracapsular		Intracapsular		
Periods	Geriatric age groups	n	%	n	%	p*
Pre-pandemic period	Youngest	146	22.8	88	26.6	0.365
	Middle	274	42.6	139	42.0	
	Oldest	222	34.6	104	31.4	
Pandemic period	Youngest	17	19.3	19	35.2	**0.038**
	Middle	40	45.5	25	46.3	
	Oldest	31	35.2	10	18.5	
*Pearson chi-square test						

a significant decrease in hip fracture admission rates during the pandemic period. Both the theories that pandemic restrictions may lead to a decrease in these fractures due to decreased activity and the theory that elderly people being indoors alone at home may lead to an increase in these fractures are acceptable. However, during the ongoing pandemic process, more precise information about the number of fractures can be obtained over a wider period of time (18). Therefore, we believe that our study provides valuable information on the fact that geriatric hip fracture rates do not change during the pandemic period.

Although geriatric fractures usually occur in low energy traumas, high energy traumas are also a frequent cause that can not be underestimated (24-26). High-velocity traumas 68.7% resulted with extra-capsular fractures (26). Furthermore, the activity levels in the youngest age seniors group are significantly higher relative to middle and oldest aged seniors (17). The difference in the fracture patterns of younger seniors could have occurred due to pandemic-related governmental restrictions. At the same time, the fracture type of hip fractures in seniors 65 years old and older remained unaltered. This situation may be the 25.4% ratio of younger seniors composition among all the old hip fractures during a pandemic. On the contrary, this shift did not result in change in fracture profiles. Under these circumstances, we believe that the information gathered does not affect the management of hip fractures during the pandemic outbreak.

Three-month mortality rates in geriatric hip fractures represent more than 50% of the deaths associated with this disease (27-29). In many studies, mortality rates during the COVID period were evaluated at 1 month (3,5,7,21,22). In addition to including a 1-year pandemic period, our study can provide broader information with 3-month mortality rates. However, there was no difference in 3-month mortality between pre-COVID and COVID periods.

Study Limitations

The study has some limitations. The first of these is that when comparing mortality rates in the study, additional diseases, ASA scoring, and other factors that may affect mortality rates are not included in the analysis. Because the abnormal distribution of these factors between pre-COVID and COVID groups may cause bias by masking the increased mortality rates that may be caused by the COVID period. The other limitations are that the study is retrospective and monocentric, and the effect of the pandemic on the postoperative functional outcomes and quality of life of these patients is not known. However, considering that its main purpose is to investigate the effect of the pandemic on fracture rates and fracture type distribution, we believe that this study provides valuable information.

CONCLUSION

Despite the restrictions imposed during the COVID-19 pandemic, there were no changes in geriatric hip fracture rates. At the same time, fracture type distribution was similar to the pre-pandemic period. When the 3-month mortality rates were compared, they were similar between the pre-pandemic and pandemic periods.

Ethics

Ethics Committee Approval: Approval was received by the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee (number: 191, date: 03.05.2021).

Informed Consent: Written informed consents were obtained from all study participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Y., M.Y., N.E., A.Ç.T., H.G., Concept: M.Y., H.G., Design: A.Y., M.A., H.G., Data Collection

or Processing: A.Y., M.Y., N.E., S.G., M.A., Analysis or Interpretation: M.Y., S.G., A.Ç.T., M.A., Literature Search: A.Y., N.E., S.G., A.Ç.T., Writing: A.Y., N.E., S.G., A.Ç.T.

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ORIGINAL ARTICLE

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Relationship Between Hematological Parameters and Follow-up and Diet Compliance in Celiac Patients

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Abstract

Objective: Celiac disease is a proximal small bowel disease developing due to persistent intolerance in people who are genetically susceptible to gluten and other gluten-like grain proteins in cereals such as mainly wheat, barley, rye, and oats. Treatment is a lifelong gluten-free diet. Strict adherence to this treatment is important for the prognosis of the disease. Since it is quite costly to follow-up of the disease, there is need to parameters that are easy to apply to reflect diet compliance and antibody level and do not require additional cost. In this study we aimed to determine whether hemogram parameters and albumin level can be used to evaluate the compliance of gluten-free diet in Celiac patients.

Methods: Fifty-seven of 133 Celiac patients whose disease was confirmed with anti-tissue transglutaminase-IgA (anti-tTG-IgA) levels were included to the study. Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), mean platelet volume (MPV), platelet distribution width (PDW), erythrocyte distribution width (RDW) and albumin levels were compared in the periods when the anti-tTG-IgA levels of the patients were positive and negative. The relationship of these results with gluten-free diet compliance was evaluated.

Results: The mean age of the patients was 38.96 (19-66). RDW value, at anti-tTG-IgA positive the period was significantly higher compared to the period when it was negative (p=0.005). PDW (p=0.02) and albumin (p=0.035) values were significantly low. Although the PLR (p=0.074) value was found to be higher, this difference was not statistically significant. There was no difference in NLR (p=0.69) and MPV (p=0.12) values.

Conclusion: PDW, RDW, and albumin levels are more cost-effective, and can be used as an auxiliary parameter to evaluate dietary adherence and antibody levels in Celiac patients' follow-up.

Keywords: Celiac disease, hematological parameters, diet compliance

INTRODUCTION

Celiac disease is a proximal small bowel disease that develops persistent intolerance to gluten and other gluten-like grain proteins in cereals mainly caused by wheat, barley, rye and oats in genetically susceptible individuals (1). Its prevalence in the population is approximately 1% (1,2). However, those diagnosed with this disease constitute 1/10-1/7 of celiac patients in the whole population (3,4). Symptoms of Celiac disease can occur in any age group (5). Gliadin, which is formed as a result of the contact of gluten with alcohol, causing small intestinal epithelial destruction and intraepithelial lymphocyte activation via IL-15 expression play role in the pathogenesis of the disease.

Gliadin's presentation to CD4 T-cells via receptor results in tissue damage by causing cytokine release. As a result, small intestinal villus atrophy and crypt hyperplasia develop. In the clinical presentation, asymptomatic people and patients with mild symptoms are more common. However, when the disease is symptomatic, often signs of malabsorption (chronic diarrhea, weight loss, bloating, fatigue) are observed. In addition to those findings, many diseases and findings

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have also been published in the literature related to Celiac disease (6,7). This disease and findings can be divided into two group as gastrointestinal and extraintestinal system diseases and findings. Atrophic glossitis, recurrent aphthous ulcers, gastroesophageal reflux, eosinophilic esophagitis, pancreatitis, autoimmune hepatitis, steatohepatitis, primary sclerosing cholangitis, inflammatory bowel disease, increased transaminase levels are findings of the gastrointestinal tract diseases and anemia (iron/B12/folate defiency), osteopenia/osteoporosis, secondary hyperparathyroidism due to vitamin D deficiency, IgA deficiency, dermatitits herpetiformis, IgA nephropathy, peripheral neuropathy due to B12 deficiency, type 1 diabetes mellitus, autoimmune thyroiditis, epilepsy, depression, migraine, infertility, short stature, delayed puberty, myocarditis, dilated cardiomyopathy, Down syndrome, Turner syndrome are part of extraintestinal findings and diseases.

Serological tests used in the diagnosis of Celiac disease are anti-tissue transglutaminase-IgA (anti-tTG-IgA), anti-endomisium-IgA, anti-deamine gliadin peptide antibodies. Definitive diagnosis is reached by endoscopically multiple biopsies samples taken from the small intestine, demonstrating intraepithelial lymphocyte increase, crypt hyperplasia and villus atrophy (8). The only known treatment is lifetime compliance with a gluten-free diet (8). It is very important to obey strict adherence to treatment in terms of prognosis and prevention of future complications.

Since the follow-up of the disease is very costly, there is a need for biomarkers that can be applied more easily and do not require additional cost, which reflect the diet compliance and antibody level of the patients. In this study, we aimed to determine whether hemogram parameters and albumin levels can be used to evaluate adherence to a gluten-free diet in Celiac patients.

METHODS

Study Design

Patients with a definitive clinical, endoscopically, and pathologically diagnosis of Celiac disease who were followed up at University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital enrolled to the study. Fifty-seven of the 133 patients with positive anti-tTG-IgA levels who attended their scheduled follow-ups and had confirmed diet adherence were included. All patients gave their informed consent. Beside the demographic and descriptive features of patients, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratios (PLR), mean platelet volume (MPV), platelet distribution width (PDW), erythrocyte distribution width (RDW) and albumin levels were compared retrospectively in periods when anti-tTG-IgA levels were positive vs. negative and their relationship with gluten-free diet compliance was evaluated.

Ethical Principles

The study was carried out after receiving approval from University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital's Ethics Committee (E-48670771-514.99), which was granted in accordance with the Helsinki Declaration of Ethical Principles.

Statistical Analysis

Data were analyzed using STATA, version 13. Mean, standard deviation, median, frequency, ratio, minimum, and maximum values were calculated and reported when applicable. Paired t-test were used for pairwise analysis of repeated measures coinciding with specific periods of the disease, and logistic regression analysis and receiver operating characteristic (ROC) analysis techniques were used for significant data associated with the disease. In addition, $p<0.05$ was considered statistically significant when interpreting the results.

RESULTS

Out of 133 Celiac patients, 76 patients did not come to regular follow-up or did not have hemogram and albumin parameters in periods when anti-tTG-IgA levels are both negative and positive. Having no definite data on dietary compliance to reflect this period was excluded from the study. Demographic and descriptive characteristics of 57 patients included in the study are shown in Table 1.

RDW value ($p=0.005$) was significantly higher during the period when the patients were anti-tTG-IgA positive, compared to the period when they were negative; PDW ($p=0.02$) and albumin ($p=0.035$) values were found to be significantly lower. PLR ($p=0.074$) value was higher however, this difference was not statistically significant. No difference was observed in MPV ($p=0.12$) and NLR ($p=0.69$) values.

Comparison of hemogram parameters and albumin levels in patients at both anti-tTG-IgA positive and negative periods are shown in Table 2.

Logistic regression analysis was performed to understand whether PDW, RDW and albumin results can predict the periods when patients' anti-tTG-IgA levels are positive and negative. The results were statistically significant at p value <0.05 significance level (*p value $=0.027$ for PDW, *p value $=0.017$ for RDW, and *p value $=0.021$ for albumin). As a result, PDW, RDW and albumin

values of the patients were found to be independent risk factors for predicting dietary compliance.

ROC analysis was performed to find the optimal cut point value of PDW, RDW, and albumin levels predicting patients' dietary compliance. In Figure 1, this ROC analysis results for parameters are shown. Area under the curve (AUC) was 0.6175 for PDW estimating dietary compliance in Celiac patients and cut-off was 15.85 (fL); for RDW, AUC was 0.6273 and cut-off was 14.25 (%); and for albumin, AUC was 0.6787 and cut-off was 44.45 (g/L).

According to these calculated cut-off values, sensitivity was 46% and specificity was 39% for PDW estimating the dietary compliance of Celiac patients. The sensitivity was 51%, the specificity was 82% for RDW; and the sensitivity was 39% and the specificity was 53% for albumin.

DISCUSSION

Clinical manifestations of Celiac disease are comparable to those of numerous other disorders. This similarity may cause a delay in the diagnosis if the disease is not suspected. Serological tests and endoscopic interventions used to evaluate dietary compliance during follow-up of patients are high-cost examinations that cannot be performed in every clinic. In this study, we aimed to determine whether hemogram parameters and albumin level can be used for the follow-up of the diet compliance of patients with Celiac disease.

Although hemogram parameters may show changes according to the etiology of the primary disease and accompanying comorbidities, they can still be utilized to forecast mortality, prognosis, disease activation, or complications that may arise in

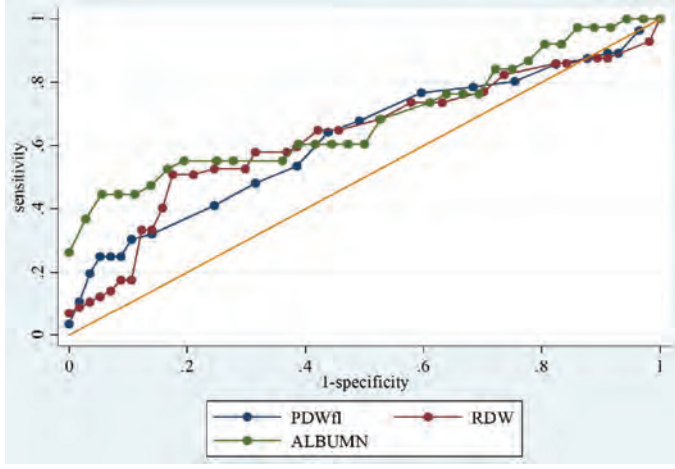

Figure 1. ROC analysis results for PDW, RDW and albumin
PDWfl: Platelet distribution width fentoliter, ALBUMN: Albumin, RDW: Erythrocyte distribution width, ROC: Receiver operating characteristic

Table 1. Demographic and descriptive characteristics

Variables		n	%
Age (years)	Min-max (median)	19-66 (39)	
	Mean ± SD	38.96±11.28	
Gender	Woman	39	68.4
	Male	18	31.6
BMI (kg/m^2)	Min-max (median)	16.6-34 (24.85)	
	Mean ± SD	24.69±3.78	
Disease (year)	Min-max (median)	0.66-21 (4)	
	Mean ± SD	4.78±4.42	

SD: Standard deviation, BMI: Body mass index, kg/m^2: Kilogram/square meter

Table 2. Comparison of hemogram parameters and albumin levels in patients at both anti-tTG-IgA positive and negative periods

Variables	Anti-tTG-IgA positive	Anti-tTG-IgA negative	*p<0.05
	Mean ± SD	Mean ± SD	p value
NLR	2.06±1.24	2.0±0.85	0.69
PLR	0.14±0.07	0.13±0.07	0.074
MPV (fL)	9.88±1.2	10.06±1.2	0.12
PDW (fL)	15.09±2.06	15.82±1.09	*0.02
RDW (%)	15.15±3.48	13.85±1.57	*0.001
Albumin (g/L)	38.48±13.24	44.68±2.62	*0.035

Anti-tTG-IgA: Anti-tissue transglutaminase-IgA, SD: Standard deviation, fL: Fentoliter, g/L: gram/Liter, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, MPV: Mean platelet volume, PDW: platelet distribution width, RDW: Erythrocyte distribution width

a many diseases. The relationship between NLR and PLR levels, which are used as markers of inflammation, with prognosis and mortality in some malignancies (9-11), Coronavirus disease-2019 infection (12,13), in the postoperative period (14,15) and in diseases acute coronary syndrome (16,17), acute ischemic stroke (18), pulmonary embolism (19) and chronic renal failure (20) has been demonstrated by meta-analysis. RDW showing anisocytosis in peripheral blood is one of the first parameters to be evaluated in the distinction between iron deficiency anemia and thalassemia. Moreover, it has been proven that increased RDW also shows poor prognosis and mortality in many diseases (21-25). Many studies have been reported in the literature demonstrating MPV and PDW which show platelet functions and activity as markers of mortality and morbidity (26-30).

There are studies about these parameters which are routinely used in practice having quite low cost compared to the serological and invasive interventions in Celiac disease.

Sarikaya et al. (31) compared 76 Celiac patients and 86 functional dyspepsia patients and reported that NLR is a sensitive test in the diagnosis and follow-up of Celiac disease. Palmacci et al. (32) examined the relationship between NLR, dietary compliance and osteoporosis in Celiac patients. Although they could not show NLR as a significant determinant of gluten-free diet adherence, they reported that it is significantly higher in Celiac patients with osteoporosis (32). In the study of Brusco et al. (33) evaluating 126 Celiac patients, increased RDW detected in 57.9% of patients as the most common hematological disorder in patients and RDW was found to be decreasing trend in 37 of 43 patients after gluten free diet. Sategna Guidetti et al. (34) reported that high RDW level despite normal hemoglobin concentration can be a reliable indicator of Celiac disease in patients with strong clinical suspicion.

CONCLUSION

In our study, we observed that PDW and RDW as hemogram parameters and albumin values which are less cost and frequently used in clinical practice can be used to evaluate the dietary compliance and antibody levels of Celiac patients during follow-up. However, there is a need for further prospective studies with a larger number of participants investigating NLR, PLR and MPV levels.

Ethics

Ethics Committee Approval: The study was carried out after receiving approval from University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital's Ethics Committee (E-48670771-514.99), which was granted in accordance with the Helsinki Declaration of Ethical Principles.

Informed Consent: All patients gave their informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.S.P., Y.G., Concept: A.S.P., Y.G., Design: A.S.P., Y.G., Data Collection or Processing: A.S.P., Y.G., Analysis or Interpretation: A.S.P., Y.G., Literature Search: A.S.P., Y.G., Writing: A.S.P., Y.G.

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CASE REPORT

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Placenta Accreata without Placenta Previa. Clinical Conservative Managment: Case Report

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Abstract

Conservative treatment and hysterectomy after cesarean section, which is the gold standard, are applied in placenta accreata spectrum (PAS) with a high maternal mortality rate. Two cases with PAS without placenta previa which was successfully treated conservatively were presented.

For diagnosis of PAS obstetricians focus on placenta previa or low-lying placenta and previous C-section history, however, 1/3 of all cases are diagnosed with PAS without placenta previa. The gold standard in the treatment of PAS is hysterectomy. In this case, conservative treatment in tertiary centers has been shown to be succesful. Obstetricians should not just focus on placenta previa. Conservative treatment modalities should be performed in tertiary centers.

Keywords: Placenta accreata spectrum, conservative treatment of placenta accreata, placenta accreata spectrum without placenta previa

INTRODUCTION

Placenta accreata is a condition resulting from abnormal invasion of the trophoblast into the myometrium (1). Placenta accreata spectrum (PAS) includes three forms: placenta increata, placenta accreata and placenta percreta graded by the invasion of the placenta. Maternal morbidity and mortality can result from severe and sometimes life-threatening hemorrhage, often requiring blood transfusions. Therefore, prenatal diagnosis is very important. Placenta accreata is often associated with factors such as endometrial injury, advanced maternal age, number of pregnancies, and increasing parity. A number of previous cesarean deliveries increase the risk of placenta accreta spectrum. There is a consensus in many literatures that PAS is seen together with placenta previa. However, the incidence of PAS is not uncommon without previa. Cesarean section followed by hysterectomy is the gold standard of PAS treatment. Conservative treatment methods are not widely used. Uterine preservation and expectant management; removal of the placental tissue, leaving uterus in place or leaving partially or totally *in situ* are the conservative treatment methods described in the literature. Informed consent was obtained from the patients.

CASE PRESENTATIONS

Case 1

The patient was 29 year-old pregnant woman with a history of gravida 2, parity 1 (presented 38 weeks and 4 dats by vaginal delivery) and no abortions. During her first pregnancy and delivery, she did not experience any complications. In the second pregnancy, the first trimester combined test aneuploidy screening test was low risk, blood pressure blood sugar, liver and kidney function tests were normal, TORCH and ELISA were negative, body mass index (BMI) was 18. In the 22nd week prenatal ultrasound scan, it was found that the normal hypoechoic region between the placenta and myometrium disappeared, there was a decrease in the retroplacental myometrial thickness (less than 2 mm) and there were a large number of vascular lacunae in the placenta. The placenta was in the anterior wall of the uterus and no previa or low-lying placenta was present Figure 1.

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Magnetic resonance imaging (MRI) was performed at 33rd week of pregnancy and the same findings were found in the ultrasound. The patient has no history of cesarean section, *in vitro* fertilization (IVF) and uterine surgery, no signs of placenta previa or low-lying placenta insertion. A 75 mg screening oral glucose tolerance test (OGTT) was performed and the result was normal. The patient had lung maturation with corticosteroids before the operation. Cesarean section performed at 37 weeks and 1 day. After the fetus was removed, the placenta inserted in the anterior surface of the uterus and the fundus was attempted to be removed manually with a halas. Before removal of the placenta, there were 2 areas on the anterior surface of the uterus, approximately 6 cm in diameter, consisting only of serosa (no endometrium and no myometrium). After the placenta was removed, the mentioned areas shrank by 1-2 cm (Figure 2).

Bilateral tubal ligation was performed at the request of the patient. Approximately 600-700 cc of bleeding was observed during cesarean section. No early complications were observed. The patient did not need any blood transfusion. The patient's entry and postoperative 6th hour hemoglobin levels were 11.6 and 10.8, respectively. The patient was discharged 48 hours after surgery.

Case 2

Twenty-nine-year-old pregnant woman with a history of 2 gravida 1 spontaneous abortion. During pregnancy, blood sugar, liver and kidney function tests were normal, TORCH and ELISA were negative, BMI was 19.5, and there is no hypertension. The first trimester combined test aneuploidy screening test was low risk. Placental location was in the fundus-posterior uterus. Prenatal level 2 screening was normal. A 50 mg screening OGTT was performed and the result was normal. Spontaneous vaginal delivery was performed by lateromedial episiotomy at 39 weeks and 3 days. It was waited for 20 minutes for the spontaneous postopartum separation of the placenta. As spontaneous separation did not ocur, ultrasonographic examination was performed and PAS was suspected. MRI was performed which revealed the PAS without placenta previa Figure 3. On MRI, the uterine thickness at the invasion site of the placenta was approximately 5 mm.

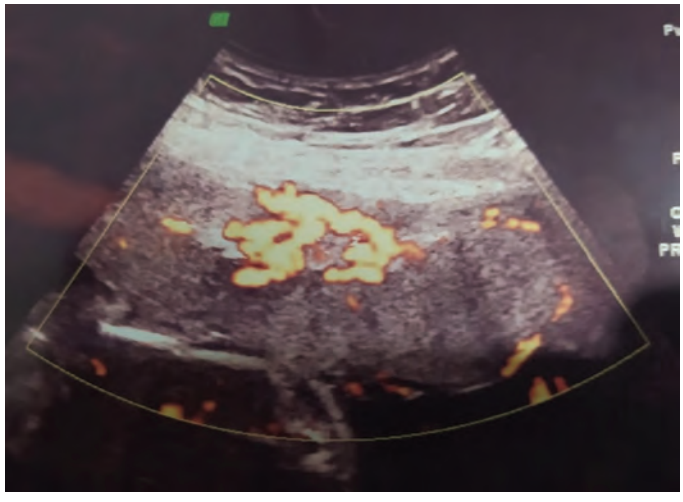

Figure 1. The placenta in the anterior wall of the uterus and show like placenta acreata spectrum

In the patient without vaginal bleeding, it was decided to apply the expectant method, which is defined as leaving the placenta completely *in situ*. Amoxicillin and clavulanate potassium 1000 g were started orally. After 5 days of hospitalization, control ultrasound revealed that the placenta size decreased to 5x6 cm and there was no bleeding. The patient was discharged and called for control every 3 days. Infection markers were detected as negative during the controls. Twenty-three days after delivery, the placenta was expelled out spontaneously. Control ultrasound showed no rest after spontan expelled placenta inside the uterus.

DISCUSSION

PAS is a term combining various degrees of abnormal trophoblast invasion into the myometrium of the uterine wall (2). Previous cesarean section, previous uterine surgery, low lying placenta and placenta previa are important risk factors for PAS (3,4). The risk of PAS increased with increasing number of cesarean deliveries (5). In both cases we presented, there was no history

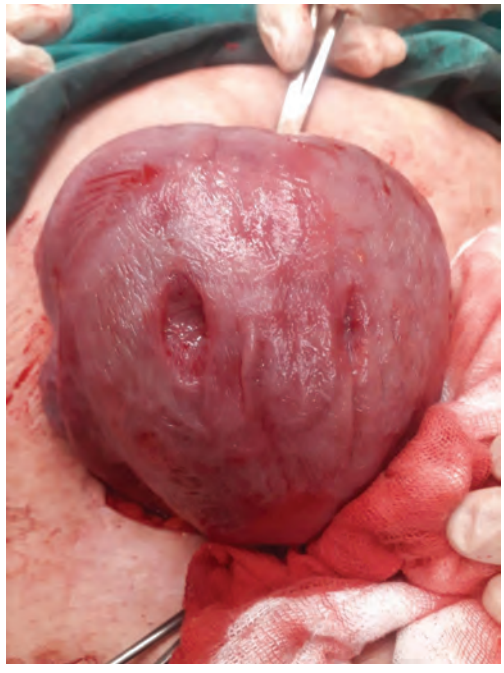

Figure 2. Uterus after removing the placenta. There are no myometrium and endometrium

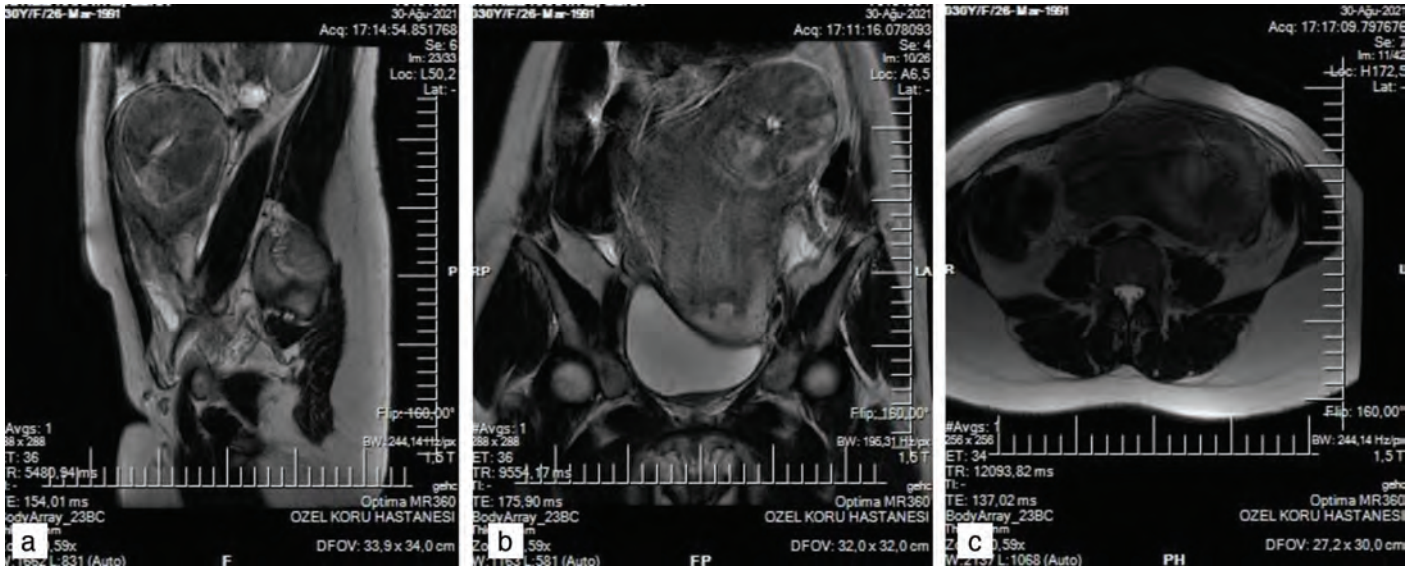

Figure 3. (a-c) Magnetic resonance imaging of the uterus with placenta postpartum 1st hours

of cesarean section, IVF, and uterine surgery, as well as evidence of placenta previa or low-lying placenta insertion. For diagnosis of PAS obstetricians generally focused on placenta previa or low lying placenta and previous C-section history, whereas some authors have shown that there were no any placenta preavia in 30% of patients with histologically spectrum of placenta accreata managed by hysterectomy (6). Some studies report that the non-previa PAS group is more likely to conceive via IVF or undergo prior operative hysteroscopy than the previa PAS group, and the incidence of classical hysterectomy is higher than the cystectomy-previa PAS group (6). Hemorrhage and severe morbidity rates were similar to patients with placenta previa. However, these patients should be referred to PAS centers for a multidisciplinary approach. Treatment of PAS is mainly consist of surgery-hysterectomy. Cesarean hysterectomy is considered the gold-standard treatment for invasive accreta (7). However, a high complication rate is observed in this form of treatment (8). Conservative treatment of PAS should be selected and decided individually for the patient. There are four different forms of conservative treatment PAS: the extirpative technique (manual removal of the placenta), the expectant approach (leaving the placenta *in situ*), one-step conservative surgery (removal of the accretal area), and the triple-P procedure (suturing around the accretal area after resection). There is insufficient evidence about the efficacy and safety of methotrexate therapy to recommend its routine use in all PAS (9) cases. Conservative treatment was preferred in both cases we presented. In case 1, as the placenta was located in the anterior fundus of the uterus, the placenta was removed and the invasion sites were sutured if necessary. Bilateral tubal ligation was performed at the request of the patient. Therefore no sutures were made. In case 2, conservative treatment modalities can be tried in appropriate patients. Since no bleeding was observed in case 2, we preferred the treatment of leaving the placenta *in situ*. Antibiotics were started against the possibility of infection, and the patient was followed closely against the possibility of bleeding. This article presents successful results of conservative treatment modalities in PAS patients. However, we argue that such treatments should only be performed in tertiary centers and that patients should be approached in a multidisciplinary manner.

CONCLUSION

Hysterectomy is one of the PAS treatment options, but only a multidisciplinary approach is performed for good patient outcomes. Conservative treatment modalities of PAS can be applied in tertiary centers and their success rates are high.

Ethics

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

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

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CASE REPORT

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A Case of Poststeroid Panniculitis After COVID-19 Infection

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Abstract

Poststeroid panniculitis is a rare complication that occurs after corticosteroids withdrawal. It is caused by the rapid discontinuation or dose reduction of steroids. Clinically, it is seen as subcutaneous nodules located in areas rich in subcutaneous adipose tissue such as cheeks and breasts. It is mostly seen in children. There are very few adult cases in the literature. As far as we know, no case has been reported after Coronavirus disease-2019 (COVID-19) infection. Here, we present a case of poststeroid panniculitis that developed after treatment discontinuation in an adult patient receiving steroids during COVID-19 treatment.

Keywords: COVID-19, poststeroid panniculitis, corticosteroids

INTRODUCTION

Coronavirus disease-2019 (COVID-19) infection, which first appeared in December 2019, is a disease that can affect many systems, especially the respiratory system. Numerous skin manifestations related to COVID-19 have been reported. Urticaria, maculopapular eruption, vasculitis are the most common ones. There are few cases of panniculitis reported after COVID-19, and they often present as erythema nodosum (1). Poststeroid panniculitis, on the other hand, is a rare panniculitis that usually develops after rapid discontinuation of steroid therapy (2). Here we present, a patient who was treated with steroids in the intensive care unit due to COVID-19 infection, who subsequently developed nodules on the face and chest, and was diagnosed with poststeroid panniculitis.

This case is presented because panniculitis may develop after COVID-19, and poststeroid panniculitis (PSP) is rare in adulthood and especially after COVID-19 infection.

CASE PRESENTATION

A 61-year-old female patient was admitted to the emergency room with complaints of weakness, loss of appetite and taste. She was diagnosed with COVID-19 with polymerase chain reaction. The patient, who was followed up in intensive care unit, was given a dose of 80 mg methylprednisolone (1 mg/kg/day) for 12 days due to respiratory distress. One week after the cessation of steroid therapy, a nodule was noticed in the right breast inferior quadrant. Breast ultrasound was performed and the patient was consulted for general surgery. A tru-cut biopsy was performed with a pre-diagnosis of granulomatous mastitis. However, biopsy was compatible with fat necrosis. Two months after discharge, the patient whose breast complaints continued was consulted to the dermatology outpatient clinic. Dermatological examination revealed a hard indurated nodule with a diameter of 6 cm on the right breast and a hard indurated nodule with a diameter of 5 cm on the right cheek (Figure 1).

Cheek and breast skin biopsies were performed with a preliminary diagnosis of PSP. Histopathological examinations revealed inflammation involving focal lipophage, focal cystic enlargements, and needle-shaped clefts in the subcutaneous lobular area. There were no signs of vasculitis (Figure 2a, 2b). The patient was diagnosed with post-steroid panniculitis with clinical and histopathological findings. Corticosteroid therapy was not

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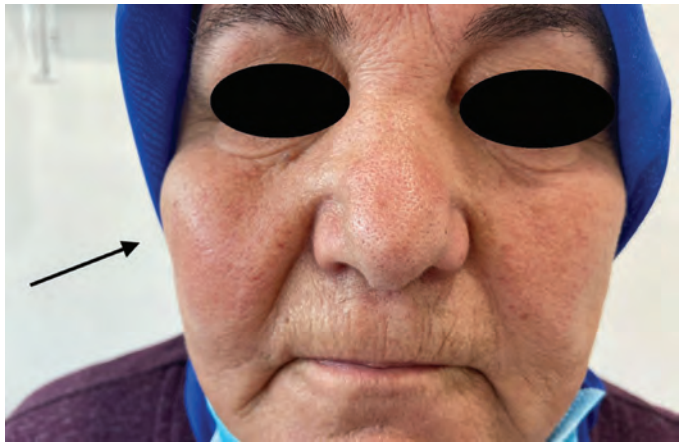

Figure 1. An indurated nodule is noticed on the patient's right cheek

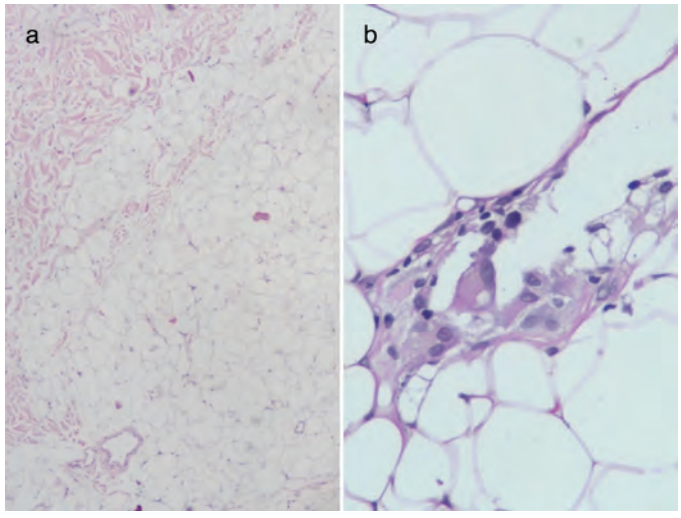

Figure 2. (a) Inflammation is seen with focal cystic enlargements in the subcutaneous lobular area. Hematoxylen eosin, x40 (b) Needle-shaped clefts are seen in the subcutaneous tissue. Hematoxylen eosin, x200

initiated because spontaneous resolution could occur, instead colchicine tablet (0.5 mg bid) was started. Partial regression was observed in the lesions during the 3-month follow-up.

DISCUSSION

The most common skin findings associated with COVID-19 have been reported as morbilliform, vesicular, urticarial, petechial rashes, transient livedo reticularis, pernio-like lesions, and ischemic acral lesions (1). There are few cases of panniculitis reported after COVID-19 infection. Eosinophilic panniculitis developed in one patient following COVID-19 infection (3). Suter et al. (4) reported that erythema nodosum may develop as a skin manifestation of COVID-19 infection.

PSP is a rare complication that develops after discontinuation of systemic corticosteroid therapy. PSP was first described by Smith and Good (2). Smith and Good (2) noticed that 11 children who received corticosteroid therapy for the treatment of various diseases such as rheumatic fever and nephrotic syndrome developed erythema nodosum-like lesions following cessation of treatment. PSP is characterized by erythematous nodules and indurated plaques that develop within days and weeks following rapid reduction or cessation of steroid dose. Nodules are especially located on the cheeks, arms and trunk (2,5). PSP shares the same histopathological findings with subcutaneous fat necrosis. These are foamy histiocytes located in the lobular subcutaneous tissue, inflammation rich in lymphocytes and needle-shaped clefts (5). Therefore, PSP can be mistakenly diagnosed as subcutaneous fat necrosis, as in our case.

PSP lesions usually regress gradually within weeks or months. Very rarely, ulceration may develop in the presence of severe disease. In case of early diagnosis, it is recommended to restart high-dose systemic steroids, then slowly decrease the dose (5,6).

There are fewer than 50 PSP cases reported in the literature, of which only 4 are adult PSP cases (6-8). As far as we know, a PSP case developing after COVID-19 infection has not been reported.

CONCLUSION

This case is presented as a reminder that panniculitis may rarely develop after COVID-19, with the exception of lesions such as erythema and urticaria. Necessary examinations in terms of panniculitis should be performed in the presence of subcutaneous nodules in patients who receive corticosteroid treatment due to COVID-19.

Ethics

Informed Consent: Informed consent form was obtained from the patient.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.U., İ.O.T., Ö.Y., Concept: İ.U., İ.O.T., Design: İ.U., İ.O.T., Data Collection or Processing: İ.U., Ö.Y., Analysis or Interpretation: İ.U., İ.O.T., Ö.Y., Literature Search: İ.U., Writing: İ.U.

Conflict of Interest: No conflict of interest was declared by the authors.

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

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ERRATUM

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The mistake has been made inadvertently by the author.

The Ethics Committee Approval information on pages 139 and 142 of the relevant article has been updated as follows:

Incorrect page 139:

Patient consent and Istanbul Yeni Yuzyil University Faculty of Medicine Ethics Committee approval were obtained in our study (decision no: 13.08.2020/**033**).

Corrected page 139:

Patient consent and Istanbul Yeni Yuzyil University Faculty of Medicine Ethics Committee approval were obtained in our study (decision no: 13.08.2020/**032**).

Incorrect page 142:

Ethics Committee Approval: Istanbul Yeni Yuzyil University Faculty of Medicine Ethics Committee approval were obtained in our study (decision no: 13.08.2020/**033**).

Corrected page 142:

Ethics Committee Approval: Istanbul Yeni Yuzyil University Faculty of Medicine Ethics Committee approval were obtained in our study (decision date and number: 13.08.2020/**032**).