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Changing Trends in Radiotherapy for Glioblastoma Multiforme and Effects on Normal Tissue Doses

Glioblastoma Multiforme Radyoterapisinde Değişen Eğilimler ve Normal Doku Dozlarina Etkileri

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ABSTRACT

Introduction: The aim of the study is to reveal the changing trends in radiotherapy (RT) for glioblastoma multiforme (GBM) from past to present and to show the changes in organs at risk (OARs) doses.

Methods: We re-planned 10 GBM patients who were previously irradiated. Rigid fusion was performed through pre- and postoperative magnetic resonance imaging (MRI) and simulation computed tomography, and 9 separate volumes were created. While volumes varied from whole brain RT (WBRT) to postoperative two-phase irradiation, RT application ranged from 2-dimensional Co-60 treatment to 3-dimensional volumetric modulated arc therapy (VMAT). OARs were contoured, and doses were noted. A 3 dimensional-conformal RT (3D-CRT) plan of the volume created by preoperative MRI was compared to 3D-CRT and VMAT plans generated by postoperative MRI. Statistical analysis was performed using Paired sample t-test.

Results: During the time of WBRT, normal brain tissue was receiving 45-60 Gy. Through VMAT, the median brain-planning target volume (PTV) D_{mean} decreased to 35 Gy. According to both PTV-Radiation Therapy Oncology Group $(RTOG)_{preop}$ and PTV-$RTOG_{preop}$ 3D-CRT plannings, there was no difference in all OARs doses between plans, including brain-PTV initial volume D_{mean} and brain-PTV boost D_{mean} doses. Significantly lower OARs doses were obtained from 3D-CRT plans based on both PTV-$RTOG_{preop}$ and PTV-$RTOG_{postop}$ volumes with the VMAT planning.

Conclusion: With changing trends in RT for GBM, there has been a significant decrease in treatment volumes and normal tissue doses. According to the postoperative volume definition of RTOG, lower normal tissue doses are obtained from VMAT plans, compared to the conformal treatment plans.

Keywords: 3D conformal radiotherapy, intensity modulated radiotherapy, glioblastoma multiforme, volumetric modulated arc therapy

ÖZ

Amaç: Çalışmanın amacı glioblastoma multiforme (GBM) radyoterapisindeki (RT) geçmişten günümüze değişen eğilimlerin ortaya konulması ve risk altındaki organ dozlarındaki değişimin gösterilmesidir.

Yöntemler: GBM tanısı ile postopereatif temozolamid ve RT ile tedavi edilen 10 hastanın simülasyon bilgisayarlı tomografi görüntüleri retrospektif olarak incelenerek pre- ve postoperatif manyetik rezonans görüntüleri (MRG) ile rjiid füzyon yapıldı ve 9 ayrı volüm oluşturuldu. Volümler total kranyum ışınlamadan postoperatif iki fazlı ışınlamaya değişkenlik gösterirken, RT uygulaması 2-boyutlu (2B) Co-60 tedavisinden 3-boyutlu (3B) volumetrik ark tedaviye (VMAT) değişiyordu. Risk altındaki organlar (organs at risk - OAR) konturlandı. Beyin-hedef hacmi planlama (PTV) D_{mean}, beyin sapı D_{max}, göz D_{max} ipsilateral/kontralateral, kiazma D_{max}, koklea D_{mean} ipsilateal/kontralateral, lakrimal gland D_{max} ipsilateral/konrtalateral, lens D_{max} ipsilateral/kontralateral, pituiter gland D_{max} dozları kaydedildi. 7, 8, 9. planlar (preop MRG'den oluşturulan volümün 3B-konformal RT-3B-KRT planı ile postop MRG'den oluşturulan 3B-KRT ve VMAT planları) karşılaştırıldı. Paired sample t-testi ile istatistiksel analiz yapıldı.

Bulgular: Total kranyum RT uygulandığı dönemlerde normal beyin dokusunun hepsi 45-60 Gy alırken VMAT ile beyin-PTV D_{mean} medyan 35 Gy'e düşmüştür. Aynı zamanda göz ve lensler dışında risk altındaki organlar verilen tüm dozu alarak 60 Gy uygulanan gruplarda doz sınırlamaları aşılmıştır. Hem PTV-Radyasyon Terapisi Onkoloji Grubu $(RTOG)_{preop}$ hem de PTV-$RTOG_{postop}$ 3D-CRT planına göre beyin-PTVinitial volüm D_{mean} ve beyin-PTV_{boost} D_{mean} dozları dahil olmak üzere tüm OAR dozlarında iki plan arasında istatistiksel anlamlı fark yoktu. VMAT planı ile hem PTV-$RTOG_{preop}$ hem de PTV $RTOG_{postop}$ volümlerine göre yapılan 3D-CRT planlarından istatistiksel anlamlı daha düşük OAR dozları elde edildi.

Sonuç: Tarihsel süreçte ışınlanan volüm ve normal doku dozlarında belirgin azalma olmuştur. RTOG'nin postoperatif volüm tanımına göre konformal ve VMAT planları karşılaştırıldığında VMAT planlamada daha düşük normal doku dozları elde edilmektedir.

Anahtar Kelimeler: 3D konformal radyoterapi, yoğunluk ayarlı radyoterapi, glioblastoma multiforme, volümetrik ark tedavisi

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Introduction

Glioblastoma multiforme (GBM) is the most deadly and frequent primary brain malignancy in adults (1). Since temozolomide was added to adjuvant radiotherapy (RT), the survival rate has improved (2). Standard treatment of GBM includes surgery, RT, and chemotherapy (3-5). RT has been routinely used in the treatment of brain tumors since the 1940s (6). The use of three-dimensional conformal radiation therapy (3D-CRT) is regarded as the standard treatment (7,8). Intensity-modulated radiation therapy (IMRT) is accepted as an alternative to 3D-CRT and it can minimize treatment-associated side effects (9). The use of proton RT is also increasing (10). Initially, RT for GBM began as whole brain irradiation. The techniques in RT have improved with the development of different doses and applications and with the determination of organs at risk (OARs) and dose limits. The aim of our study was to reveal the changing trends in RT for GBM from past to present and to show the changes in OARs doses.

Methods

Simulation computerized tomography (simCT) and cranial magnetic resonance imaging (MRI) scans of 10 patients, who were treated with adjuvant temozolomide following concomitant temozolomide and RT after surgical resection, were selected from patient database of İstanbul University Institute of Oncology Hospital. After the selection, previous basic scans of the patients were called back to the RT simulation station. No patient actually joined to the simulation process and neither names nor any identifying information related to the study population were used. Due to the retrospective and simulative nature of our study, no informed consent and no ethical approval were obtained. However, the study was performed in compliance with the Declaration of Helsinki. A rigid fusion was performed through MIM software ver. 6.5 (MIM Software Inc., Ohio, USA) using simCT images, pre- and postoperative contrast-enhanced T1 and T2/flair sequences MR images. OARs and dose constraints were determined according to the European Organization for Research and Treatment of Cancer-Advisory Committee on Radiation Oncology Practice guide and the study of Scoccianti et al. (11,12). Optic chiasm, bilateral eyes, bilateral lenses, brainstem, bilateral cochlea, bilateral lacrimal glands, and pituitary gland were determined as the OARs. Brain-planning target volume (PTV) volume was generated through PTV excluded from brain tissue. In two-dimensional planning (2D), fields were manually created using multi-leaf collimators. Two-phase target volumes yielded from pre-operative MR images were determined according to the Radiation Therapy Oncology Group (RTOG) 9710 protocol. The $RTOG_{preop}$ phase 1 volume contained the volume of contrasted tumor with peripheral edema on preoperative MRI scan plus a 2 cm extra-margin. The $RTOG_{preop}$ boost volume covered the contrasted lesion (without edema) on the preoperative MRI scan plus a 2.5 cm extra-margin. The $RTOG_{postop}$ phase 1 volume included the volume of the postoperative cavity and +/- residual tumor in contrast enhanced T1-weighted MRI scans and edema in the postoperative T2-weighted MRI scans plus a 2 cm margin. The $RTOG_{postop}$ boost volume included the resection cavity +/- residual tumor in contrast enhanced T1-weighted MRI scans plus a 2 cm margin. 2D treatment planning was used to create plans 1 to 6. 3D planning was made in plans 7 to 9. Plans 7 and 8 were performed through 3D-CRT, whereas plan-9 was generated through VMAT. The XIO v4.60 treatment planning system was used for all plans except the VMAT plan. The Eclipse V8.9 treatment planning system (Varian Medical Systems, Palo Alto, CA, USA) was used for VMAT. Treatment plans were prepared with 3 full rotation VMAT fields with different collimator angles. VMAT doses were prescribed according to ICRU 83.

Co-60 was used for generating plans 1 and 2, and 6 MV was used for the remaining plans. Plan 1: Whole brain RT (WBRT), Co-60 energy, total dose 45 Gy in 25 fractions (fr); Plan 2: WBRT, Co-60 energy, total dose 60 Gy in 30 fr; Plan 3: WBRT, 6 MV energy, total dose 45 Gy in 25 fr; Plan 4: WBRT, 6 MV energy, total dose 60 Gy in 30 fr; Plan 5: WBRT in phase 1 followed by tumor bed boost in phase 2, 6 MV energy, phase 1 dose 40 Gy in 20 fr plus boost dose 20 Gy in 10 fr; Plan 6: PTV-$RTOG_{preop}$ phase 1, 6 MV energy, phase 1 dose 46 Gy in 23 fr plus boost dose 14 Gy in 7 fr; Plan 7: PTV-$RTOG_{preop}$ phase 1, 6 MV energy, 3D-CRT, phase 1 dose 46 Gy in 23 fr boost dose 14 Gy in 7 fr, Plan 8: PTV-$RTOG_{postop}$ phase 1, 6 MV energy, 3D-CRT, phase 1 dose 46 Gy in 23 fr plus boost dose 14 Gy in 7 fr; Plan 9: PTV-$RTOG_{postop}$ phase 1, 6 MV energy, VMAT, 46Gy in 23 fr plus boost 14 Gy in 7 fr. Brain-PTV D_{mean}, brainstem D_{max}, bilateral eye D_{max}, optic chiasm D_{max}, bilateral cochlea D_{mean}, bilateral lacrimal gland D_{max}, bilateral lens D_{max}, and pituitary gland D_{max} doses were recorded. The plans 7, 8 and 9 were compared.

Statistical Analysis

SPSS software version 20 was used for the statistical analysis (IBM Corp., Armonk, NY, USA) using the paired sample t-test. A p value <0.05 was considered statistically significant.

Results

Through VMAT, the median brain-PTV D_{mean} decreased to 35 Gy while all normal brain tissues received 45-60 Gy. At the same time, the OARs, except for the eye and the lenses, received overdoses in groups given 60 Gy. In Figure 1, the changes in four parameters of 9 plans are presented. Because both PTV-$RTOG_{preop}$ and PTV-$RTOG_{postop}$ had large treatment volumes, 3D-CRT planning was possible using two opposing coplanar fields. There was no statistically significant difference between the two plans for all OARs doses, including brain-PTV phase 1 D_{mean} and brain-PTVboost D_{mean} doses. In addition, optic chiasm D_{max}, bilateral cochlea D_{mean}, brainstem D_{max}, pituitary gland D_{max}, bilateral eye D_{max} median dose values were over the dose constraints. The PTV-$RTOG_{preop}$ 3D-CRT, PTV-$RTOG_{postop}$ VMAT plans were compared; doses of brain-PTV phase 1 D_{mean} (median 41.7 Gy vs. 24.1 Gy, p=0.001), brain-PTV boost D_{mean} (median 44 Gy vs 34.4 Gy, p=0.021), chiasm D_{max} (62.1 Gy vs. 52.9 Gy, p=0.030), contralateral cochlear D_{mean} (median 59 Gy vs. 13.8 Gy, p=0.002), ipsilateral cochlear D_{mean} (median 61 Gy vs. 28.5 Gy, p=0.006) and contralateral eye D_{max} (median 36.2 Gy vs. 23.2 Gy, p=0.022) were statistically lower in the $RTOG_{postop}$ VMAT plan. The lens D_{max} doses were within dose constraints except for one value in both groups, although the $RTOG_{postop}$ VMAT dose was higher in the lens D_{max} dose (median 3.9 Gy vs. 7.9 Gy, p=0.005). The PTV-$RTOG_{postop}$ 3D-CRT plan was compared to PTV-$RTOG_{postop}$ VMAT; the doses of Brain-PTV initial D_{mean} (median 43.5 Gy vs. 24.1 Gy, p<0.001), brain-PTV boost D_{mean} (median 45.5 Gy vs. 34.4 Gy,

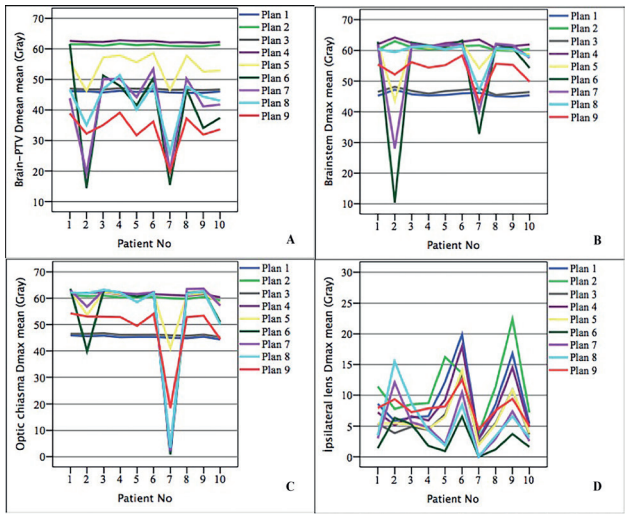


Figure 1. The doses of four organs at risk generated from 9 different plans

Plan 1: Whole brain radiotherapy (WBRT), 2D planning, Co-60, total dose 45 Gy in 25 fractions; Plan 2: WBRT, 2D planning, Co-60 energy, total dose 60 Gy in 30 fractions; Plan 3: WBRT, 2D planning, 6 MV energy, total dose 45 Gy in 25 fractions; Plan 4: WBRT, 2D planning, 6 MV energy, total dose 60 Gy in 30 fractions; Plan 5: WBRT in phase 1 and tumor bed in phase 2, 2D planning, 6 MV energy, phase 1 dose 40 Gy in 20 fractions plus boost dose 20 Gy in 10 fractions; Plan 6: planning target volume (PTV)-Radiation Therapy Oncology Group ($RTOG)_{preop}$, 2D planning, 6 MV energy, phase 1 dose 46 Gy in 23 fractions plus boost dose 14 Gy in 7 fractions; Plan 7: PTV-$RTOG_{preop}$, 3D planning, 6 MV energy, 3D-CRT; phase 1 dose 46 Gy in 23 fractions plus boost dose 14 Gy in 7 fractions; Plan 8: PTV-$RTOG_{postop}$, 3D planning, 6 MV energy, 3D-CRT, phase 1 dose 46 Gy in 23 fractions plus boost dose 14 Gy in 7 fractions; Plan 9: PTV-$RTOG_{postop}$, 3D planning, 6 MV energy, VMAT, phase 1 dose 46 Gy in 23 fractions plus boost dose 14 Gy in 7 fractions

p<0.001), optic chiasm D_{max} (62 Gy vs. 52.9 Gy, p=0.029), contralateral cochlea D_{mean} (median 48.3 Gy vs. 13.8 Gy, p=0.029), ipsilateral cochlea D_{mean} (median 57.2 Gy vs. 28.5 Gy, p=0.002), brainstem D_{max} (median 60.4 Gy vs. 55.3 Gy, p<0.001), pituitary gland D_{max} (median 61.4 Gy vs. 46.7 Gy, p=0.005), contralateral eye D_{max} (median 40.1 Gy vs. 23.2 Gy, p=0.007), and contralateral lacrimal gland D_{max} (median 36.4 Gy vs. 22.1 Gy, p=0.0232) were statistically lower in the $RTOG_{postop}$ VMAT plan. 3D-CRT, made in two phases according to PTV $RTOG_{preop}$ and $RTOG_{postop}$ volumes, and the OARs doses, made in two phase VMAT plan according to the $RTOG_{postop}$ volume, are given in Table 1.

Discussion

The routine use of RT in brain tumors began in the 1940s with kilovoltage X-rays (13,14). In the 1960s, 45-60 Gy RT was applied to the entire brain with megavoltage X-rays or Co-60 teletherapy devices (15,16). We found that all the OARs and whole brain tissue received a median [standard deviation (SD)] dose of 45 (3) Gy, except for lenses, when 45 Gy WBRT was delivered after 2D planning through Co-60 or linear accelerators. The lenses were the only normal tissue that could be protected with protection blocks anatomically because of being away from the brain tissue. In 1979, Walker et al. (13) found that 50-60 Gy doses were associated with increased survival when compared with doses ≤45 Gy. In those days, 50 - 60 Gy was applied to the whole brain. When we performed 60 Gy 2D WBRT with Co-60 and linear accelerators, we found that all the OARs and the whole brain were receiving a median (SD) dose of 60 (3) Gy, except for the lenses. All of the OARs exceeded the dose constraints that need to be considered today. In the 1970s, some centers were delivering an initial dose of 30-46 Gy as WBRT, followed by 20-30 Gy irradiation to the tumor bed, so two-phase treatment was used (17-21). Initially, CT (in the 1970s and 1980s) and then MRI (in the late 1980s) was used for delineating RT target volumes (22). Afterwards, two-phase treatment plans including phase 1 and boost volumes were used by abandoning WBRT. Previously, two-phase target volumes were created with the aid of preoperative imaging, predominantly considering preoperative tumor and edema volumes. In this study, we compared two different two-phase plans using 6 MV energy through WBRT (40 Gy/20 fr) + boost (20 Gy/10 fr), PTV-$RTOG_{preop}$ phase 1 (46 Gy /23 fr) + PTV-RTOGboost (14 Gy/7 fr) volumes generated according to RTOG 9710. Between these two plans, there were no significant differences in terms of Brain-PTVinitial D_{mean}, chiasm D_{max}, and brainstem D_{max} doses. However, in the plans generated according to RTOG 9710, the brain-PTV boost D_{mean}, contralateral cochlear D_{mean}, contralateral eye D_{max}, contralateral lacrimal gland D_{max}, ipsilateral lacrimal gland D_{max}, contralateral lens D_{max}, and ipsilateral lens D_{max} doses were significantly lower, so normal OARs were better spared. In addition to technological advances, approaches in generating irradiation volumes for GBM were changing in accordance with clinical evaluations. The side effects of RT in neurological tissues have led to this change. Brain irradiation is associated with neurotoxic side effects including radionecrosis and cognitive impairment (23,24). For the first time, Chang et al. (25) compared the RTOG volume, including peritumoral edema in preoperative MRI and target volumes in which peritumoral edema is not taken into consideration, but in which the residual tumor in the postoperative MRI +/- is targeted. According to both RTOG and MD Anderson Cancer Center plans, they revealed that 90% of the recurrences were central and within the area. Today, guidelines recommend using a postoperative MRI while defining/delineation target volume for RT in GBM. Different cooperative groups have target volume delineation that includes or excludes peritumoral edema (26). In this study, we compared the 3D-CRT plan of preoperative volume based on RTOG, the 3D-CRT plan of postoperative volume based on RTOG, and the VMAT plan of postoperative volume based on RTOG. The doses of OARs obtained in the VMAT plan, made in two phases according to PTV-$RTOG_{preop}$ and PTV-$RTOG_{postop}$ volumes, and made in two phases according to the $RTOG_{postop}$ volumes with 3D-CRT and brain-PTV initial / boost D_{mean} were significantly lower. Although 3D-CRT is accepted as the standard in general use, IMRT and VMAT use are increasingly used in tumors with large volume and near OARs (9-11). 3D-CRT is often sufficient in cases of spherical frontal or parietal tumors, whereas more successful plans can be made with IMRT or VMAT in irregularly shaped brainstem or near-orbit-like tumors (27,28). VMAT is usually preferred, because it provides a faster treatment plan and treatment application with conformality similar to IMRT. Today, the dose to be preferred in a young patient, who is fit and whose performance score is good, is 60 Gy in 30 fractions with concomitant temozolomide (11). Hypofractionated schedules are suitable for elderly or patients with a poor performance status (such as 40 Gy in 15 fractions or 34 Gy in 10 fractions) (29,30).

Conclusion

RT for disease control of GBM is important. With changing trends in RT for GBM, there has been a significant decrease in the treatment volumes and normal tissue doses. Today, the volume is generated according

Table 1. Comparison of normal tissue doses generated from 3 different radiotherapy plans according to Radiation Therapy Oncology Group volumes

	A Mean (SD) median (min-max)	B Mean (SD) median (min-max)	C Mean (SD) median (min-max)	A-B p value	A-C p value	B-C p value
Brain-PTV phase I D_{mean}	39.6 (12) 41.7 (18.1-52.4)	40.2 (8.4) 43.5 (22.6-48.7)	24.3 (3.3) 24.1 (16.9-28.5)	0.693	0.001	<0.001
Brain-PTV boost D_{mean}	41.4 (12.2) 44 (19.3-53.4)	42.9 (7.6) 45.5 (25.8-51.4)	33.6 (5.6) 34.4 (19.8-39.1)	0.458	0.021	<0.001
Optic chiasma D_{max}	55.5 (18.9) 62.1 (2.2-63.6)	54.8 (18.5) 62 (3.4-63.2)	48.6 (11) 52.9 (18.5-54.3)	0.463	0.030	0.029
Contralateral cochlea D_{mean}	42.2 (28.1) 59 (0.7-60.9)	38.4 (22.2) 48.3 (1.7-56.8)	12 (6.9) 13.8 (2.3-20.2)	0.183	0.002	0.001
Ipsilateral cochlea D_{mean}	43.6 (29.3) 61 (0.6-63)	42.7(25.3) 57.2 (1.5-60.8)	22.9 (11.5) 28.5 (2.8-33.5)	0.624	0.006	0.002
Brainstem D_{max}	55.8 (11.9) 61.6 (28-62.1)	59 (4.4) 60.4 (47-61.4)	53.6 (4.3) 55.3 (43.2-58.4)	0.349	0.484	<0.001
Pituitary gland D_{max}	48.1 (24.4) 62.1 (1.8-63.1)	53.5 (18.6) 61.4 (2.4-62.6)	41.9 (12.6) 46.7 (15.1-51.8)	0.289	0.151	0.005
Contralateral eye D_{max}	35 (21.3) 36.2 (0.1-58.4)	37.9 (21) 40.1 (0.2-60)	23.4 (9) 23.2 (7.9-38.2)	0.097	0.022	0.007
Ipsilateral eye D_{max}	38.3 (23.5) 41.3 (0.1-62.6)	42 (22.8) 46.5 (0.2-62.3)	34.5 (13.2) 35.7 (8.5-49.4)	0.100	0.333	0.053
Contralateral lacrimal gland D_{max}	30.3(21) 34.3 (0.2-58.2)	32.4(20.5) 36.4 (0.2-60)	21.9(8) 22.1 (10.1-35.5)	0.166	0.079	0.032
Ipsilateral lacrimal gland D_{max}	35.7 (23.6) 40.6 (0.1-61.4)	39.9 (22.9) 47.6 (0.2-62.2)	32.3(10.6) 36.5 (9.8-44)	0.063	0.475	0.095
Contralateral lens D_{max}	5.9 (4.2) 5.4 (0.06-12.7)	6.2 (4.2) 6 (0.1-15.3)	7.7(2) 7.7 (4.2-11.9)	0.619	0.084	0.183
Ipsilateral lens D_{max}	5.1(3.8) 3.9 (0.05-12)	5.5(4.4) 3.9 (0.1-15.5)	7.9(2.3) 7.9 (4.4-12.5)	0.415	0.005	0.066

A. Radiation Therapy Oncology Group $(RTOG)_{preop}$, Two-phase conformal radiotherapy plan using preoperative volumes according to RTOG 9710; B. $RTOG_{postop}$, Two-phase conformal radiotherapy plan using postoperative volumes according to actual RTOG recommendations; C. $RTOG_{postop}$, Two-phase volumetric modulated radiation therapy plan using postoperative volumes according to actual RTOG recommendations; X: mean value, SD: standard deviation, PTV: planning target volume, min-max: minimum-maximum

to the post-operative cranial MRI in the target volume delineation. When conformal and VMAT plans are compared according to the post-operative definition of RTOG, lower normal tissue doses are obtained in VMAT plans. 3D-CRT can be used depending on tumor location, while VMAT is advantageous when the treatment volume is close to OARs.

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

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