



Original research

Correlation of peripapillary nerve fiber layer thickness with visual outcomes after decompression surgery in subclinical and clinical thyroid-related compressive optic neuropathy

Mohammad Taher Rajabi, Mina Ojani*, Hamid Riazi Esfahani, Seyed Zia Tabatabaei, Mohammad Bagher Rajabi, Seyede Simindokht Hosseini

Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran

Received 20 April 2018; revised 8 October 2018; accepted 5 November 2018

Available online 21 December 2018

Abstract

Purpose: To assess the correlation of peripapillary retinal nerve fiber layer (PRNFL) thickness with visual recovery in compressive optic neuropathy (CON) in patients with thyroid eye disease (TED).

Methods: Twenty-three eyes of 13 consecutive patients with TED-related CON were prospectively recruited. Assessment of PRNFL by means of spectral domain optical coherence tomography (SD-OCT), visual field (VF) parameters, color vision, and visual acuity in logMAR were compared before and 6 months after decompression surgery in the operated eye for each patient, which in ten cases included both eyes. Decompression surgery was performed as medial and inferior wall decompression sparing the orbital strut by the same surgeon.

Results: There was a significant correlation between the preoperative PRNFL average thickness and postoperative improvement in visual acuity among all patients ($P = 0.048$). This correlation was found to be significant in clinically non-edematous optic neuropathy cases ($P = 0.023$) but not in edematous optic neuropathy ($P = 0.23$). There was significant correlation between PRNFL thickness and improvement of postoperative mean deviation (MD) and pattern standard deviation (PSD) parameters in VF studies and in color vision scores ($P = 0.005$, $P = 0.02$, $P = 0.01$, respectively). Average PRNFL thickness and quadrantal PRNFL were all significantly reduced after decompression surgery in all of the cases ($P = 0.024$).

Conclusions: PRNFL thickness measured by SD-OCT is correlated with visual recovery after decompression surgery in TED-related CON. In eyes with severe VF defect (MD worse than -10 dB), the ones with higher preoperative PRNFL thicknesses (>65 μm) had more improvement in MD compared with those with thin PRNFL measures (<60 μm).

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Keywords: Retinal nerve fiber layer thickness; Optical coherence tomography; Decompression surgery; Thyroid eye disease; Compressive optic neuropathy

Introduction

Thyroid eye disease (TED) is an autoimmune orbital inflammatory disease. Typical orbital signs and symptoms are consisted of eyelid retraction, proptosis, ocular motility

dysfunction, chemosis, congestion of episcleral and conjunctival blood vessels, lagophthalmos, and orbital pain.^{1,2}

Near 5% of TED patients may experience severe complications like compressive optic neuropathy (CON) and exposure keratopathy.³

CON can cause permanent vision loss if not detected timely.^{1–3} Clinical findings in CON include decreased visual acuity, impaired color vision, and visual field (VF) loss. A relative afferent pupillary defect may be present in asymmetric involvement of the optic nerves.⁴

Conflict of interest: Authors declare no financial support or relationships that may pose conflict of interest.

* Corresponding author.

E-mail address: ojani_mina@yahoo.com (M. Ojani).

Peer review under responsibility of the Iranian Society of Ophthalmology.

The mechanism of CON begins with muscle enlargement or increased retro-bulbar fat volume. Steroid therapy, orbital radiation, and surgical decompression are different modalities for management of CON.⁵ Although each of these interventions carries its own risks and benefits, surgical decompression has been revealed to have higher success rates.⁶ Although it is well recognized that visual improvement may occur after surgical decompression, visual recovery is highly unpredictable.⁷ Previous studies have shown that the peripapillary retinal nerve fiber layer (PRNFL) is affected in compressive optic neuropathies of various causes.⁸ Alteration in the neuronal mass in the retina especially in peripapillary area seems to have direct and indirect effects on the visual function. The peripapillary nerve fiber mass can influence the VF parameters.⁹ Compressive pathologies, edema from any cause, or atrophic processes may change thickness of the retinal nerve fiber layer (RNFL) and may affect the visual prognosis of that pathological process. Treatment modalities that target these pathologies may affect the RNFL thickness and visual outcomes in a reversible phase. Actually, PRNFL thickness is a quantitative measure that provides an objective estimation of remaining viable ganglion cells axonal mass. After the relief of the compressive effect, the edema and stasis are relieved, and this can possibly improve the optic nerve function and visual parameters. Decreased PRNFL thickness seems to be an indicator of visual recovery following medical and surgical interventions in CON patients.⁹

Optical coherence tomography (OCT) is a non-invasive imaging that utilizes low-coherence interferometry for obtaining cross-sectional images of the retinal layers and optic nerve head,¹⁰ and it is valuable specifically for evaluation of RNFL thickness. Spectral domain OCT (SD-OCT) has a much faster scan rate and higher resolution (<5 μm) than previous generations of OCT.¹¹

Various studies have made this hypothesis come into mind that the thickness of peripapillary and macular nerve fiber layer quantified by OCT imaging would be associated with visual outcome in CON.^{7,9,12}

In CON caused by TED, edema of the neural mass can be detectable in funduscopy of some patients by finding the optic nerve head in an edematous state. On the other hand, in some of the thyroid-associated CON patients, especially in early stages of the disease, optic nerve head edema is hardly detectable in funduscopy even though the compressive effect is detectable in various amounts in the orbital CT-scan and mild degrees of aggravated visual acuity, decreased color vision, or present relative afferent pupillary defect are detectable in the examination. We investigated whether there was any quantitative measure to put an indication for surgical decompression or not. PRNFL thickness decrease after decompression surgery may be a quantitative measure with predictive value of final visual outcome in these patients. The aim of this study was to assess the correlation of PRNFL thickness values with visual acuity, VF global parameters (mean deviation (MD) and pattern standard deviation (PSD)) and color vision after decompression surgery in CON in TED.

Methods

Fifteen consecutive patients with CON due to TED were prospectively recruited. These patients were referred by general ophthalmologists to the Orbit and Oculoplasty Department of Farabi Eye Hospital, Tehran University of Medical Sciences. The Institutional Review Board/Ethics Committee approved the study. This research adhered to the tenets of the Declaration of Helsinki. We included TED patients with one or more of these conditions: decreased vision (more than 2 lines), dyschromatopsia identified by Ishihara plates, related VF defects, or relative afferent pupillary defect. Orbital CT-scan of sagittal and axial planes was performed to confirm compressive effect on optic nerve.

Patients with any type of glaucoma, dense cataract, optic neuropathy from unrelated cause, any previous medical treatment or radiotherapy, high myopia, moderate to severe diabetic retinopathy, and any previous signs of optic atrophy were excluded from the study.

Before surgery, the following data were collected: visual acuity, slit-lamp biomicroscopy findings, applanation intraocular pressure measurement, color vision (using Ishihara pseudo isochromatic plates), exophthalmos (measured by Hertel exophthalmometer), and VF sensitivity as measured by static perimetry (Humphrey Visual Field Analyzer 2, Carl Zeiss Mediate, Inc., Dublin, California, USA) using the Swedish Interactive Threshold Algorithm standard test 24-2 strategy.

OCT mapping was performed using SD-OCT (Spectralis® Heidelberg Engineering, Heidelberg, Germany) to measure PRNFL. All PRNFL circular scans were performed by one examiner using the Spectralis SD-OCT system (software version 5.1.2; Heidelberg Engineering GmbH). The Spectralis SD-OCT system provides an algorithm to determine the inner and outer limits of the RNFL in the peripapillary area. For interpretation of the PRNFL thickness map, the optic disc was segmented to 6 sectors as follows: temporal (T, 315–45°), nasal (N, 135–225°), superior temporal (TS, 45–90°), superior nasal (NS, 90–135°), inferior nasal (NI, 225–270°), inferior temporal (TI, 270–315°), together with an averaged global classification (G) demonstrated in the center of the circle. Green areas show the 95% normal range found in healthy subjects of the same age, whereas values outside the 99% confidence interval (CI) of the normal distribution ($0.01 < P < 0.05$) are indicated in red. Yellow areas represent values outside the 95% CI but within the 99% CI of the normal distribution as a borderline status.¹³

Trans-conjunctival inferior orbitotomy approach in combination with trans-caruncular medial orbitotomy was the selected approach for decompression surgery. All orbital procedures were done under general anesthesia by the same surgeon (M.T.R.).

Trans-caruncular incision was made to expose the medial orbital wall just behind the posterior lacrimal crest. A vertical incision was made in the medial wall periosteum to reach the bone surface; a periosteum elevator was then used to dissect the periorbital. Then the medial wall was opened, and a

complete ethmoidectomy was performed. Ethmoidal vessels were cauterized, and bone and periosteal removal was done all the way to the optic foramen. For the inferior trans-conjunctival approach, the lower eyelid was retracted downwards, the conjunctiva and lower lid retractors were cut from the lateral canthus to the caruncle, and prolapsing preseptal orbital fat was dissected step by step. The periosteum was incised and separated from orbital floor. The orbital floor was removed from approximately 1 cm posterior to the orbital rim to the posterior border of the maxillary sinus. Then periorbita was opened all the way from anterior to posterior in multiple incisions and then dissected with long scissors to enable herniation of fat and muscles in medial and inferior walls. If possible, we tried to remove fat both in medial and inferior walls. The orbital strut that is the bony junction of the maxillary sinus and the ethmoid sinus was spared to prevent inferomedial displacement of the globe.

Six months after surgery, visual acuity, color vision, exophthalmos, and intraocular pressure was measured. Slit-lamp biomicroscopy and fundus examination was performed. PRNFL OCT and VF study were performed for all the cases.

The OCT and VF parameters, color vision score, and visual acuity data in logMAR were compared before and 6 months after decompression surgery in the operated eye for each patient, which in ten cases included both eyes.

Statistical analysis

Wilcoxon rank sum test was used to compare visual acuity, VF parameters, and PRNFL thickness measures before surgery and at the postoperative visit. The OCT instrument database color-coded values were used to determine normal PRNFL thickness. PRNFL thickness changes were analyzed separately in clinically edematous and non-edematous discs by Paired *t*-test. Pearson's correlation coefficient was used to determine whether a linear correlation was present between preoperative PRNFL thickness and postoperative visual improvement and between PRNFL thickness and VF parameters. In multivariate analysis, general estimating equations (GEE) were used to take into account the fact that eyes within the same subject were being analyzed. All statistical analyses were performed with SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). *P* values less than 0.05 were considered statistically significant. Mean values are demonstrated by mean \pm standard deviation (SD).

Results

Fifteen consecutive TED-related CON patients were recruited in this prospective study. Twenty-six eyes met the study criteria; three eyes of two patients were excluded because of inability to perform VF tests properly due to low vision. Thus, 23 eyes of 13 patients, 10 with bilateral and three with unilateral optic neuropathy, were included in data analysis.

The mean age of patients was 50.48 ± 8.77 (range, 35–67 years). The mean duration of follow-up was 11.6 months (range, 6.5–13.1 months). Twelve eyes belonged to the female

cases (52% of the eyes). Baseline mean visual acuity was 0.24 ± 0.24 logMAR, and color vision was $73 \pm 0.24\%$ based on Ishihara pseudoisochromatic palates (Table 1). Mean amount of MD was -6.56 ± 6.8 , and mean PSD was 5.12 ± 3.26 on preoperative VF tests.

The mean preoperative PRNFL thickness was 116.78 ± 30.11 μ m. Eyes classified as having normal PRNFL thickness identified significantly more Ishihara color plates correctly than did the eyes with thin PRNFL (65.0% vs. 45.2%, *P* = 0.026). In addition, eyes with normal PRNFL thickness at baseline had less severe VF defects before surgery (*P* = 0.001). Thin preoperative PRNFL thickness also was associated with worse final visual acuity and VF parameters (*P* = 0.001).

In funduscopic examination of optic nerve head, seven eyes had clinically edematous and sixteen eyes had non-edematous optic nerves. There was no statistically significant difference between these two groups in terms of age (*P* = 0.55), gender (*P* = 0.75), and length of follow-up (*P* = 0.22). The postoperative improvement in visual acuity, color vision, MD, and PSD was statistically significant in both groups (Table 1). Improvement of best corrected visual acuity (BCVA) was not statistically significant between the two groups of clinically edematous and non-edematous optic nerves (*P* = 0.70).

Among patients with preoperative visual acuity of 0.30 logMAR or better, 94% remained in this category after surgical decompression, and in the six patients whose preoperative visual acuity was worse than 0.30 logMAR, four attained acuity of 0.30 logMAR or more.

There was significant reduction in PRNFL thickness in all quadrants except inferior quadrant. In the presence of clinically edematous discs, there was statistically significant higher reduction of PRNFL thickness in all quadrants postoperatively

Table 1

Pre and postoperative measures of visual acuity, exophthalmos (measured by Hertel exophthalmometer), color vision (percent of identified Ishihara plates), mean deviation (MD), pattern standard deviation (PSD), and peripapillary retinal nerve fiber layer (PRNFL) thickness in different quadrants. *P* value shows the significance of each parameter changes after surgery.

	Preoperative	Postoperative	<i>P</i> -value
BCVA (logMAR) (Median \pm SD)	0.22	0.4	0.004
Exophthalmos (mm) (Median \pm SD)	25	21	0.001
Color Vision (percent)	84	92	0.001
MD (Median \pm SD)	-3.42	-1.62	<0.001
PSD (Median \pm SD)	4.01	2.24	<0.001
Average PRNFL thickness (microns)	108	97	<0.001
Superior quadrant PRNFL thickness (microns)	142	121	<0.001
Inferior quadrant PRNFL thickness (microns)	152	129	<0.001
Nasal quadrant PRNFL thickness (microns)	93	74	<0.001
Temporal quadrant PRNFL thickness (microns)	78	65	<0.001

BCVA: Best corrected visual acuity; MD: Mean deviation; PSD: Pattern standard deviation; PRNFL: Peripapillary retinal nerve fiber layer; SD: Standard deviation.

Table 2

Peripapillary retinal nerve fiber layer (PRNFL) thickness changes in non-edematous and edematous discs after surgery.

	Non-edematous discs		Edematous discs	
	Mean \pm SD	<i>P</i> -value	Mean \pm SD	<i>P</i> -value
Average PRNFL change (microns)	-7.35 ± 1.99	0.002	-53.47 ± 26.27	0.002
Superior quadrant PRNFL change (microns)	-5.31 ± 1.73	0.008	-65.14 ± 40.18	0.005
Inferior quadrant PRNFL change (microns)	-2.13 ± 1.20	0.740	-79.85 ± 40.44	0.002
Nasal quadrant PRNFL change (microns)	-4.18 ± 1.25	0.500	-51.00 ± 28.54	0.003
Temporal quadrant PRNFL change (microns)	-3.62 ± 0.80	0.001	-24.28 ± 15.67	0.006

PRNFL: Peripapillary retinal nerve fiber layer; SD: Standard deviation.

in this group (Table 2). Average PRNFL thickness and quadrantal PRNFL thickness were all significantly reduced after surgery ($P = 0.024$) (Table 1).

We found a correlation between the preoperative PRNFL average thickness and postoperative improvement in visual acuity among all patients although this correlation was significant based on Pearson's correlation coefficient with borderline *P* values ($P = 0.048$). This correlation was found to be significant in non-edematous optic neuropathy cases ($P = 0.023$) but not in the eyes with edematous optic neuropathy in fundus exam ($P = 0.23$).

There was also significant correlation between PRNFL thickness and postoperative improvement of MD, PSD, and color vision ($P = 0.005$, $P = 0.02$, $P = 0.01$, respectively). A non-linear relationship was observed between the preoperative PRNFL thickness and absolute change in perimetric MD in all quadrants. This relationship was also obvious between preoperative PRNFL thickness and PSD in all quadrants except the temporal (Table 3).

In eyes with significant VF defects (MD worse than -10 dB), in cases with higher preoperative PRNFL thicknesses (>65 μ m), there was 5.8 ± 1.3 dB improvement in MD compared with those with thin PRNFL measures (<60 μ m) who improved on average by only 2.6 ± 1.7 dB ($P = 0.001$). Eyes, which had 8 dB or more improvement in MD, had a mean PRNFL thickness of 117.2, compared to a mean PRNFL thickness of 56.5 μ m in eyes that had lower MD improvement ($P = 0.001$).

Discussion

In this study, we showed that BCVA, MD, and PSD in VF study and color vision significantly improve after decompression surgery in patients with TED-associated CON. There

was no statistically significant difference between clinically edematous and non-edematous optic neuropathies, in visual improvement and all of the cases demonstrate one or more of the aspects of visual improvement when the compressive effect is relieved. These results are consistent with the results of other studies about decompression surgery outcomes in other various causes of CON.^{5,14}

This correlation was not detected in edematous optic neuropathy group as a linear correlation. Clinical trend was improvement of visual function, but due to higher baseline PRNFL thickness, this correlation could not reach a statistical significance.

Park et al. evaluated the influence of optic nerve compression on the PRNFL thickness in eyes with acute and chronic dysthyroid optic neuropathy (DON). They concluded that the mean temporal PRNFL thickness was thinner in eyes with chronic DON compared to eyes with acute DON and control eyes. They also showed an association between thicker inferior PRNFL thickness and better visual outcome.¹⁵

In a recent study of Park et al., in 2018, they analyzed PRNFL with OCT in patients with DON before and 1 and 6 months after orbital wall decompression and compared the results with the control eyes. The study design was similar to our study, and the results were comparable with our study. They demonstrated a significant decrease in global average, superior, temporal, and inferior PRNFL thickness 1 and 6 months after decompression surgery. Their data was also in support of their previous study about the association of greater preoperative inferior PRNFL thickness and better postoperative visual acuity at the last visit.¹⁶

There are also studies suggesting the use of OCT preoperatively to estimate visual recovery after orbital decompression in orbital pathologies other than TED. In these studies, patients with pituitary adenomas underwent OCT imaging

Table 3

Correlation between preoperative peripapillary retinal nerve fiber layer (PRNFL) thickness in each quadrant and best corrected visual acuity (BCVA), mean deviation (MD), and pattern standard deviation (PSD).

		Preoperative average PRNFL thickness	Preoperative superior quadrant PRNFL thickness	Preoperative inferior quadrant PRNFL thickness	Preoperative nasal quadrant PRNFL thickness	Preoperative temporal quadrant PRNFL thickness
MD Changes	Pearson Correlation	0.682	0.810	0.681	0.599	0.088
	<i>P</i> -Value	0.005	0.000	0.000	0.003	0.688
BCVA Changes	Pearson Correlation	-0.388	-0.245	-0.356	-0.480	-0.271
	<i>P</i> -Value	0.048	0.260	0.045	0.020	0.210
PSD Changes	Pearson Correlation	-0.482	-0.598	-0.401	-0.543	-0.061
	<i>P</i> -Value	0.020	0.003	0.058	0.007	0.784

PRNFL: Peripapillary retinal nerve fiber layer; MD: Mean deviation; BCVA: Best corrected visual acuity; PSD: Pattern standard deviation.

preoperatively. Patients with the average thickness of the PRNFL more than 75–80 μm were demonstrated to have excellent visual recovery after surgery^{7,17} that was comparable with our findings.

PRNFL thinning is presumably due to axonal loss caused by chronic compression of the optic nerves. It is presumed that visual dysfunction is irreversible in a patient with a thin PRNFL after permanent loss of the axons in visual pathway. On the other hand, in a patient with normal PRNFL thickness, impaired visual function may be due to reversible causes, such as axoplasmic stasis or slow axonal conductivity, and patients in this category have more chance for vision recovery after decompression.¹⁸ In the current study, there was also a significant correlation between PRNFL thickness and post-operative improvement of color vision and retinal sensitivity in perimetry. Eyes with normal PRNFL thickness had generalized improvement in the VF parameters (MD and PSD) after decompression surgery.

Various studies have achieved conflicting results for post-operative visual outcome prediction. Some studies have identified PRNFL thickness as a predictor of visual outcomes in VF parameters after decompression surgery in different orbital pathologies.^{19,20}

Rebolleda et al., in 2009 showed a significant relationship between PRNFL decrease and improvement in VF global indices (MD and PSD) in patients with mild papilledema in idiopathic intracranial hypertension. There was also a relationship at baseline between PRNFL and MD in a way that for every 10 microm of mean RNFL thickness increase at baseline, there was a 0.6 dB decrease in MD at the last follow-up.⁹

Danesh-Meyer et al. have shown that patients with paraschiasmal tumors that had poor visual acuity or VF parameters but normal PRNFL before surgery had a significantly greater chance for recovery of MD and BCVA than those with thin PRNFL in the same preoperative level of visual function.⁷ Another study of pituitary adenoma patients noted that a higher preoperative PRNFL thickness increased the probability of complete recovery of the VF defects after surgery. This effect was independent of age or duration of symptoms.¹⁷ These results are comparable with our results in CON due to TED. In the presence of advanced VF defects, patients with higher PRNFL thickness showed more improvement in visual function whereas patients with thin PRNFL in this group, demonstrated significantly less improvement in VF parameters and visual acuity outcomes. Therefore, PRNFL thickness seems to be a good predictor for improvement of VF parameter and acuity outcome in the presence of advanced VF defects. Using OCT, the average PRNFL thickness in normal eyes has been reported to vary from 90 to 128 μm . Ajtony et al. found an average PRNFL thickness of $96.48 \pm 8.24 \mu\text{m}$ in their normal group of cases.²¹ However, there is a wide range of variability between normal populations. Therefore, there should be a baseline PRNFL OCT for each TED patient if they are going to be monitored in this way that makes it possible to recognize early stages of disc edema or atrophy in these patients. In 2016 Mugha et al. evaluated the retinal

nerve fiber layer thickness profile in thyroid ophthalmopathy in patients without any clinical sign of optic nerve dysfunction. In two measurements which were 6 months apart, average RNFL thickness was significantly lower than the control group. Interestingly, the thickness of inferior quadrant decreased significantly after 6 months which the authors considered a continuous subclinical RNFL damage.²² This finding is in contrast with our results that showed a subclinical RNFL edema in DON patients. This can be easily explained with the compressive nature of DON which causes a decrease in axonal flow in the early disease before the clinical atrophy happens. One feasible way to evaluate the axonal damage in edematous optic nerves would be evaluation of macular ganglion cell complex which many studies showed to be an earlier indicator of neuronal loss.²³

A cat model study²⁴ showed that animals that lost many nerve fibers required a long time to recover, so our 6-month follow-up in some patients might be short for investigation of final recovery. On the other hand, as the occurrence of optic atrophy and pallor does not require a long time, we think 6 months of follow-up can be considered acceptable.

In Carter et al.'s²⁵ study about transantral-ethmoidal decompression outcomes in CON due to Grave's ophthalmopathy, patients with better preoperative visual acuity had a better visual prognosis. Our findings on BCVA were similar to this study as 94% of patients with BCVA better than 20/40 Snellen chart (0.3 logMAR) remained in this category after decompression surgery. From six patients with preoperative visual acuity worse than 0.3 logMAR, four attained acuity of 20/40 or better. Baseline acuity in the CON is an important prognostic predictor of vision in eyes with CON.

The time lapse between very early stages of CON and further stages might be very short time. In some cases, in a short period of time, a mild impaired color vision in the form of red desaturation, turns into a full blown edematous optic nerve head by impaired visual acuity and relative afferent pupillary defect that leads to permanent sequelae. Early diagnosis of minimal compressive effects on the optic nerve saves us time to make decision for decompression surgery and prevent permanent visual defects.

Our data on PRNFL thickness shows a significant reduction after decompression surgery in either edematous or non-edematous discs. This finding is persistent even in normal-appearing discs on examination. It can be postulated that there is a subclinical PRNFL edema even in normal-appearing discs due to direct compression of the apical portion of the optic nerve by enlarged extraocular muscles, which causes ischemia of the retinal ganglion cell axons and disruption of axonal transport.

One of the limitations of this study is instrumental error. Patients with CON of any cause may have poor fixation due to severe diminished visual acuity; therefore, we used strict reliability criteria and excluded patients with unreliable VFs to minimize this effect. We performed two separate OCT scans at each visit with the average of the two being used in the analysis. Other limitations of our study are its small sample size and relatively short duration of follow-up.

In conclusion, PRNFL thickness is correlated with visual recovery after decompression surgery in TED-related CON. In eyes with significant VF defect (MD worse than -10 dB), the ones with higher preoperative PRNFL thicknesses (>65 μm) had more improvement in MD compared with those with thin PRNFL measures (<60 μm). We recommend further investigation on the role of ganglion cell layer analysis by OCT in the setting of TED-related CON that may be used to detect early neuron loss and help identify patients that need more aggressive treatment.

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