Visualizing patients treated with Three-Dimensional Computed Tomography-Guided Brachytherapy

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Abstract

This paper focuses on visual data mining methods for prostate cancers. The most common cancer among US men is prostate cancer. It is estimated that in the year 2002, 189,000 US men were diagnosed with prostate cancer, of which 30,200 died. Even with these alarming numbers, there is still no universally agreed-upon strategic plan for the diagnosis and management of prostate cancer. One of the contributing factors to why there is no universal treatment of prostate cancer is because treatment requires individualized care. Depending on the details of the prostate cancer, such as severity, locality, recurrence, patient age, patient life expectancy, etc..., a particular treatment method or cocktail of management care is prescribed. In this paper, we explore these variables using the CrystalVision data mining tool.

1. Introduction and background

The most common cancer among US men is prostate cancer. It is estimated that in the year 2002, 189,000 US men were diagnosed with prostate cancer, of which 30,200 died.[1] Even with these alarming numbers, there is still no universally agreed-upon strategic plan for the diagnosis and management of prostate cancer. One of the contributing factors to why there is no universal treatment of prostate cancer is because treatment requires individualized care. Depending on the details of the prostate cancer, such as severity, locality, recurrence, patient age, patient life expectancy, etc…, a particular treatment method or cocktail of management care is prescribed.

1.1 Risk factors for prostate cancer

The risk factors for prostate cancer may involve age, race, geography, family history, dietary fat, vasectomy, and sexual activity. In regards to age, white male over 50 who have no family history of prostate cancer, African American men at age 40, or men of any age who have

a first-degree relative with prostate cancer are at risk. In regards to race, African American men have an incidence of prostate cancer 1.5 that of white men, while China and Japan populations have the lowest rates. In regards to geography, prostate cancer is highest in Scandinavian countries and lowest in Asia. In regards to family history, men who have a first-degree relative with prostate cancer have twice the increased risk for prostate cancer. Although dietary fat and vasectomy have been linked to an increased risk for prostate cancer, there is no link found between sexual activity and the disease.[1]

1.2 Clinical indicators of prostate cancer

Prostate cancer can be rated clinically based on three factors, prostate-specific antigen (PSA) level, Gleason's score, and staging. For all three factors, a higher the score means poorer prognosis of prostate cancer. PSA is a molecule produced by the prostate, and is the ultimate indicator of successful treatment. When the prostate is under a cancerous stage, it will produce a significantly higher level of PSA. PSA level is determined through blood sample and its value range continuously above 0.0 ng/mL; a normal PSA is < 4.0 ng/mL, and men with PSA ≥ 4.0 ng/mL are recommended for digital rectal exams (DRE) and/or prostate biopsy. After a patient has been treated for prostate cancer with radiation therapy (e.g. external-beam radiation therapy and prostate brachytherapy), biochemical disease-free survival is defined by the American Society for Therapeutic Radiology and Oncology (ASTRO) Consensus Panel (ACD) as having a nadir PSA of 0.1 ng/mL for at least two years and having no three consecutive rises above the nadir PSA after two years.[6]

Gleason's score is based on biopsy or tissue sampling of the cancer, and ranges from 2 to 10—whole numbers only—with 10 being most severe. The Gleason system recognizes primary and secondary cell morphology patterns, and the addition of both scores is the Gleason score. The mature cells of prostate cancer will have a picture of low grade, and the more aggressive immature cells high grade. For example, a primary pattern may have grade 4 and a secondary pattern may have grade 3—the Gleason score will be 7 (4 + 3).

Prostate cancer staging is based on the TNM system which characterizes the size of the primary tumor (T), extent of nearby lymph node (N) involvement, and presence or absence of metastasis (M). The TNM system was developed by the International Union against Cancer in cooperation with the American Joint Committee on Cancer.[7] Tumor staging is based the locality

of the prostate cancer, and patients are classified, in order of severity, T1a, T1b, T1c, T2a, T2b, T3a, T3b, and T4. In the T1a – T2a stages, the prostate cancer is relatively localized in the prostate, in the T2b – T3b stages, the prostate cancer extends throughout the prostate and invaded the seminal vesicle, (e.g. seminal vesicle), and in the T4 stage, the prostate cancer has spread to adjacent organs.

1.3 Treatments

The treatment of prostate cancer can be categorized as follows: clinically localized disease, recurrence of prostate cancer, locally advanced disease, advanced systemic disease, and treatment of medical emergencies.

In clinically localized disease, the prostate cancer is localized to the prostate. In such case, the following methods are used to treat and monitor the cancer: watchful waiting, radical prostatectomy, radiation therapy, and hormonal therapy. Watchful waiting is appropriate for patients whose cancer has been detected at an early stage, the amount of cancer is relatively small, and the cancer is not highly aggressive. Patients under watchful waiting undergo rectal exams, PSA test, and biopsy at regular intervals to monitor their cancer. Radical prostatectomy is the complete removal of the prostate gland and surrounding tissues, and is used when the cancer is aggressive. Radiation therapy is also used to treat aggressive prostate cancer, and there are many types, including external-beam radiation therapy (EBRT), conformal EBRT, intensity-modulated radiotherapy (IMRT), interstitial radiotherapy, and high-dose-rate (HDR) devices. EBRT is the traditional method of radiation therapy, and sends out radiation targeted at the prostate and surrounding tissue. Conformal EBRT creates a three-dimensional representation of the target structures and designs a high radiation dose that conforms to the shape. IMRT is a recently developed technique, and improves upon conformal EBRT by delivering a highly non-uniform beam to create greater conformal dose distributions. Interstitial radiotherapy, often referred to as “radioactive seeds,” involves permanently placing radioactive iodine-125 (^{125}I) or palladium-103 (^{103}Pd) in the target area. Whereas interstitial seeds deliver low-dose-rate radiotherapy, HDR devices deliver high-dose-rate temporarily to the target area.

Recurrence of prostate cancer is when patients undergo initial prostate cancer treatment but show sign of rising prostate cancer activity after treatment. Patients with recurrence of prostate cancer often are advised to seek alternative care treatment such as hormonal therapy, salvage surgery, observation, or experimental therapy.

In patients with locally advanced prostate cancer, they are advised to use EBRT with or without HDR interstitial therapy, androgen ablation with EBRT, radical prostatectomy with or without adjuvant therapy, or regular radiation therapy. EBRT with or without HDR interstitial therapy has been described above. Androgen ablation is the deprivation of the male body of androgen, a set of hormones, of which testosterone is most prevalent, closely linked to some forms of prostate cancer cells. Androgen ablation is used to induce apoptosis, cell death, while EBRT is used to control the cancer. Radical prostatectomy and regular radiation therapy has been described above.

In advanced systemic disease of prostate cancer, there are four classes of treatment methods: first-line therapies for advanced disease, second-line hormonal therapies, chemotherapy for hormone refractory disease, and radiation for palliating bone metastasis. In first-line therapies for advanced disease, the patient has not responded to local treatment efforts or presents an advanced form of the disease that cannot be treated with surgery or radiation therapy. First-line therapies include surgical or medical castration. The testes produce about 95% of the testosterone in human males, and bilateral orchiectomy, surgical castration, reduces the plasma level of testosterone by 93%. Chemical castration is accomplished through the use of LHRH analogs or anti-androgens to regulate the release of LH or block the effects of androgens at the prostate tissue level, respectively. Second-line therapies include the use of hormones to regulate and control prostate cancer, and include the following drugs, flutamide, aminoglutethimide, and ketaconazole. Chemotherapy for hormone-refractory disease includes the use of more drugs such as mitaxantrone and estramustine. Radiation for palliating bone metastasis has been described above.

Lastly, the treatment of medical emergencies in patients with prostate cancer is rare. Patients with prostate cancer that compromises the spine are advised to seek MRI or CT scans. They are also advised to undergo one of the treatments discussed above.

2. Three-Dimensional Computed Tomography-Guided Brachytherapy

Three-dimensional computed tomography-guided brachythreapy (3DCTGB) is a FDA-approved technique developed by Dr. Panos Koutrouvelis at the Uro-Radiology Prostate Institute (URPI) in 1995 to treat prostate cancer. The technique has been previously reported.[5] Under the classification of treatments we outlined above, 3DCTGB is an interstitial treatment, using ^{125}I or ^{103}Pd. This technique has several advantages over alternative treatments, including but not limited to, a pararectal (back) approach, non-surgical, precision, an outpatient procedure, and ability to treat difficult cases of prostate cancer. Traditional prostate cancer treatments often use a perineal (the perineum is the area between the scrotum and anus) approach, whereas, 3DCTGB uses a pararectal approach avoiding soft tissue and sensitive areas. 3DCTGB is also non-surgical, and does not involve the removal of any tissue, much less, the prostate, which is often a critical component of patient preference for treatment. The advances of 3DCTGB include coupling CT visual imaging to guide, in real-time, and verify radioactive seed. The prostate is visualized in three-dimensions and radioactive seeds are placed in the appropriate dose. Traditional techniques such as EBRT are not able to exclusively target the prostate. 3DCTGB is a one-day walk-in-walk-out procedure, lasting only from one to three hours at most. Perhaps most importantly, 3DCTGB is able to treat difficult cases of prostate cancer, such as in patients with extensive seminal vesicle invasion, calcification, TURP defect, large glands, and in patients without rectum.

2.1 The patient dataset

The dataset we are working on consists of 673 patient records that were treated between June 1, 1994 and June 30, 2002—courtesy of Dr. Koutrovelis—with 3DCTGB as the initial treatment (there were no previous treatment for prostate cancer). Of the 673 patients, only 539 patient records had enough follow-up PSAs to be used for biochemical analysis—and

consequently, also for our visual analysis. Each patient must have at least three PSA entries covering at least two years post-treatment to be classified as success or failure for the treatment (success or failure has been described above by the ACD).

Table 1 summarizes the clinically relevant patient characteristics of all patients (n = 673), such as age, initial PSA, Gleason's scores, stages, and types of seeds used to treat the patients. The table also shows the range for PSA, initial prostate volume, and age.

Table 2 summarizes the patients' biochemical-disease free survival (n = 539). As can be seen in table 2, patients are categorized into risk profiles of high, intermediate, and low risk. High risk patients are at risk in terms of all three prostate cancer indicators: PSA, Gleason's score, and Stage (see Clinical indicator of prostate cancer section above). Intermediate risk patients are at risk for only 1 risk factor. Low risk patients are still at risk but their risk factors have relatively low scores. Each risk profile is further stratified according to the three risk factors. In Table 2, the risk factors and their required conditions are bolded and presented first. It can be seen from Table 2 that overall, patient success rate or the number of patients with no biochemical evidence of disease is high, at 94% (507 patients out of 539) for patients who undergo 3DCTGB. Table 2 also confirms the intuition that low risk patients will have the highest success rate, followed by intermediate risk patients, and then high risk patients.

Table 3 is a Kaplan-Meier plot of the patients for each risk profile (n = 539), and the curves were compared using the log-rank test. As can be seen, there are statistical significance differences between the survival rate of high-low risk patients and high-intermediate risk patients, $p = 0.001$ and $p = 0.037$, respectively. The Kaplan-Meier plot shows the survival rate of the patients over time, while the biochemical profile shows a snapshot of the disease-free survival rate for all patients according to their last three PSA values. As can be seen from Table 3, all patients who fail under 3DCTGB do so before 5 years. Patients who exhibit no sign of recurrence of cancer after 4 years usually remain free of cancer for the rest of their lives.

2.2 Analysis—Introduction

As can be seen from Tables 2 and 3, 3DCTGB has a high success rate for all patients in general. Our concern was not only to investigate the correlation between the variables that determine successful patients, but also to investigate what types of patients would fail 3DCTGB. As a guideline, we used Dr. Wegman's brush-tour techniques with Crystal Vision, scatter plot matrix, and the theory of color to help explore the dataset.[2] For the interested reader, the additive color scheme we used is: red + green = yellow, red + blue = magenta, green + blue = cyan, and red + green + blue = white. The complimentary color pairs are red and cyan, green and magenta, and blue and yellow.[2]

2.3 Analysis—Crystal Vision and the patient dataset

For Crystal Vision, we exported the 539 patient records for visual analysis. Each record had the following 6 attributes: initial PSA, age, Gleason's score, stage, initial prostate volume, and an indicator—designated as ***ev*** or ***event***—of whether the patient was successful or failed biochemically from being treated with 3DCTGB. For further analysis, we also exported the records according to risk profile—high, intermediate, and low risk—with the same attributes.

2.4 Analysis—Patients who failed under 3DCTGB

Figure 1 shows a parallel coordinate plot of the 539 patients; patients who failed are colored in cyan, and patients who were successful are colored in green. From Figure 1, it is difficult to characterize successful patients from those who failed. As a result of this difficulty, we cropped out successful patients and focused on patients who failed. Figure 2 shows all the patients that failed under 3DCTGB. From the parallel coordinate, we can see that there were two groups of patients who failed, those with low initial PSA values, colored in red, and those with high initial PSA values, colored in green. Figure 2 suggests that the variable with the least variance between these two groups is stage. From Figure 2, we conjecture that patients who failed 3DCTGB show great variance in all the variables, but show a high correlation with stage; patients in a late stage of prostate cancer may not successfully undergo 3DCTGB. Figure 3 reinforces the statements made about Figure 2.

2.5 Analysis—Patients who were successful under 3DCTGB

Figure 4 shows a parallel coordinate plot of all patients who were successful under 3DCTGB. There were 7 clusters defined by the stage axis, and they were colored, red, green, blue, yellow, cyan, aqua, and brown, for stages T1a, T1b, T1c, T2a, T2b, T3a, and T3b. Figure 4 shows that whereas stage was important for determining which patients failed under 3DCTGB, a low initial PSA is important for determining which patients were successful under 3DCTGB. A scatter plot matrix diagram will also show that a low initial prostate volume is also important for successful treatment under 3DCTGB in Figure 5.

2.6 Analysis—The three risk profiles: high, intermediate, and low risk patients

The three risk profiles of patients were plotted in parallel coordinates and scatter plot matrix to further investigate the relations of the variables in determining failure or success. In Figures 6 – 9, successful patients are colored in red, and patients who failed are colored in green. Figure 6 show that high risk patients who failed 3DCTGB have both a high Gleason's score and stage. There is one outlier, however, who failed with a low stage but high Gleason's score. Further analysis (not shown) discovered that this patient had a high initial PSA value and Gleason's score. In Figure 7, we also see that intermediate risk patients who failed also have a high Gleason's score and stage. Again, in Figure 8, we see that the one low risk patient who failed under 3DCTGB also had a high Gleason's score and stage. Figure 9 is a scatter plot matrix of high risk patients with Gleason's score versus stage. Figure 9 confirms the statement made about Figure 6, however, with the scatter plot matrix view, we see that there is one patient who failed in the lower left hand corner with a low Gleason's score and stage. Upon further analysis (not shown), we discovered that this patient lied at the extreme of old age.

It must be said that in general, Figures 6 – 9 suggest a combination of high Gleason's score and stage are characteristic of patients who failed. However, old age alone or a high initial PSA value in combination with a high Gleason's score may also lead to failure of treatment under 3DCTGB—as is shown by the outliers. At the same time, we see that many patients who were successful also had a high Gleason's score and stage. In fact, successful patients showed

great variability between all variables, which supports the statistics of Table 2 that 94% of all patients, regardless of risk profile, were successfully treated with 3DCTGB.

3. Discussion

Since 3DCTGB has a high success rate in treating all patients, the scientific investigation into the characteristics of patients who failed became more interesting to our research than trying to understand successful patients. In general, it can be said that patients who failed 3DCTGB (with the treatment as their first prostate cancer treatment), show a high Gleason's score and stage. Outliers indicate that old age or a high initial PSA may also play a role in contributing to patients who failed. On the other hand, in general, patients who were successfully treated under 3DCTGB shared a low initial PSA value. Future work may include the use existing clustering algorithms, in particular, clustering algorithms that can handle mixed data (discrete and continuous variables), and rule-production systems to confirm/verify the visual clustering methodology used here.

4. Conclusion

There are many treatment options for prostate cancer; however, we focus on 3DCTGB due to its ability to treat difficult cases. Reports of 3DCTGB have been favorable in terms of long-run outcomes for low, intermediate, and high risk patients. We explore not only the shared characteristics among successful patients, but we also investigated visually why patients fail treatment under 3DCTGB. Successful patients tended to have lower initial PSA values, while those who failed showed a tendency to have a higher stage coupled with an additional risk factor.

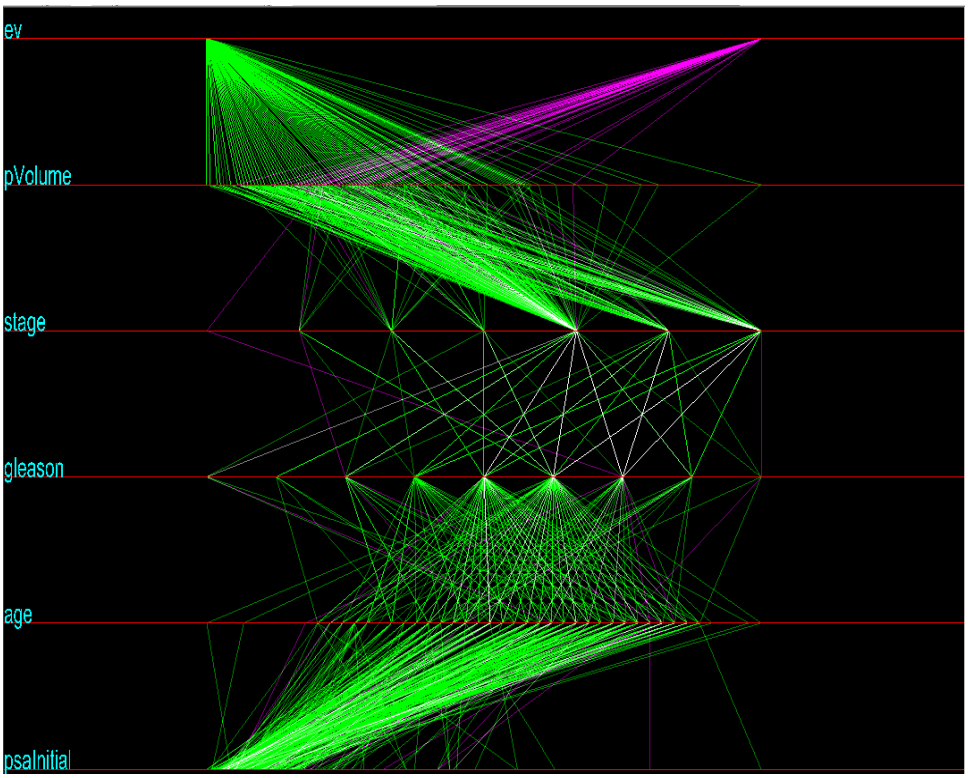

Figure 1. Parallel coordinate plot of 539 patients treated with 3DCTGB. We are using complimentary colors green and magenta. Patients who failed are colored in cyan, and patients who were successful are colored in green. White regions are where cyan and green overlap.

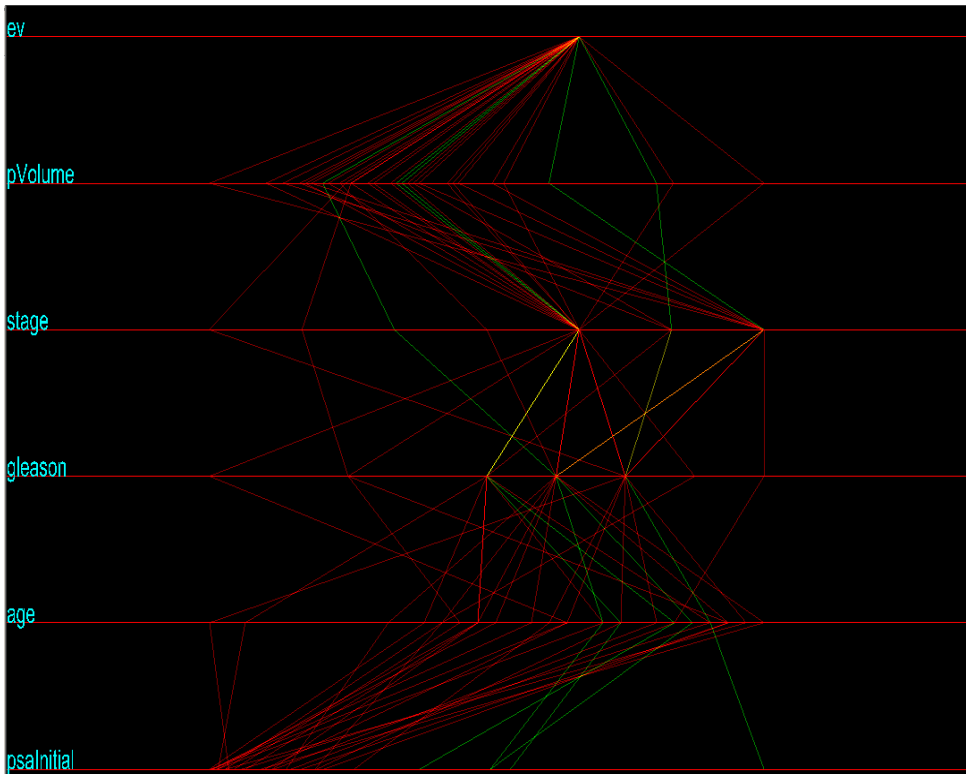

Figure 2. A parallel coordinate plot of all patients who failed under 3DCTGB. There are two clusters of patients who failed—those with a low initial PSA, colored in red, and those with a high initial PSA, colored in green. All the variables show great variance except for the stage variable.

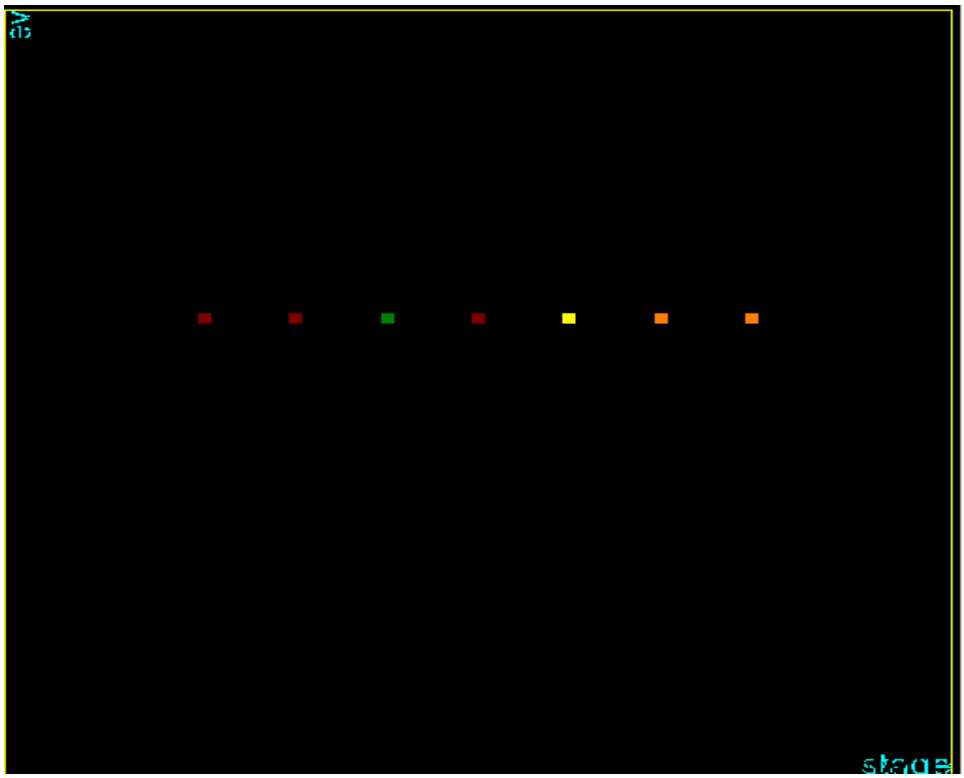

Figure 3. A scatter plot matrix diagram showing event versus Gleason's score of all patients who failed 3DCTGB. Red represents patients with low initial PSA values, and green represents patients with a high initial PSA value. As can be seen here, there is visual correlation between a late stage and failure, shown in yellow.

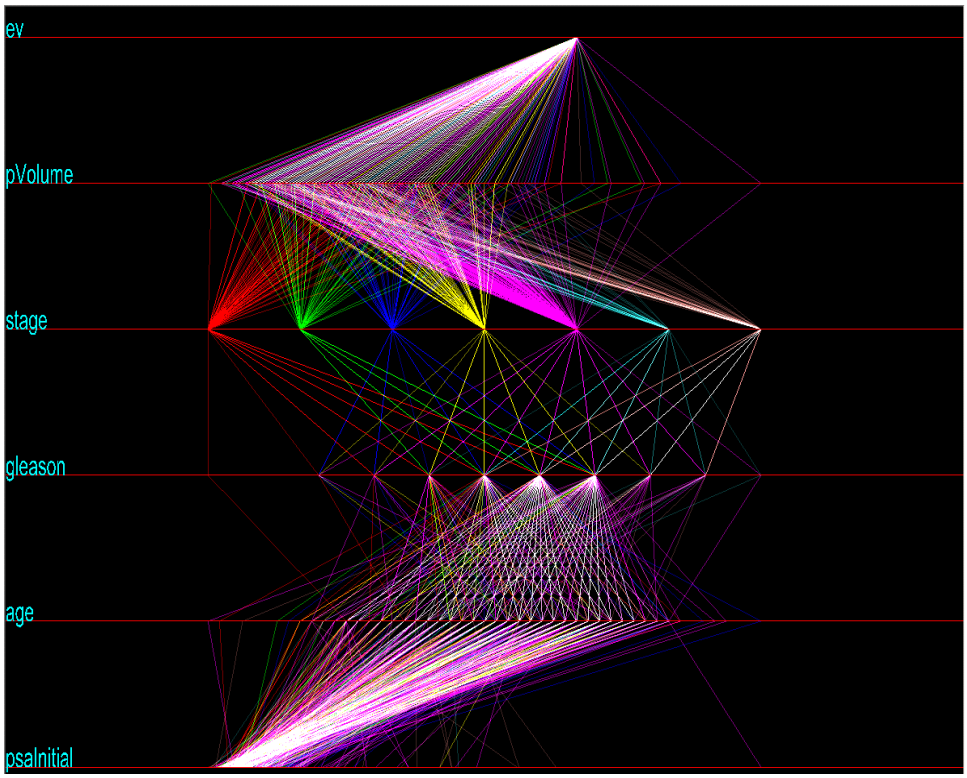

Figure 4. A parallel coordinate plot of all patients who were successful under 3DCTGB. Each stage, T1a, T1b, T1c, T2a, T2b, T3a, and T3b, were colored with red, green, blue, yellow, cyan, aqua, and brown, respectively. There are overlapping areas along the axis of initial PSA and prostate volume, shown in white.

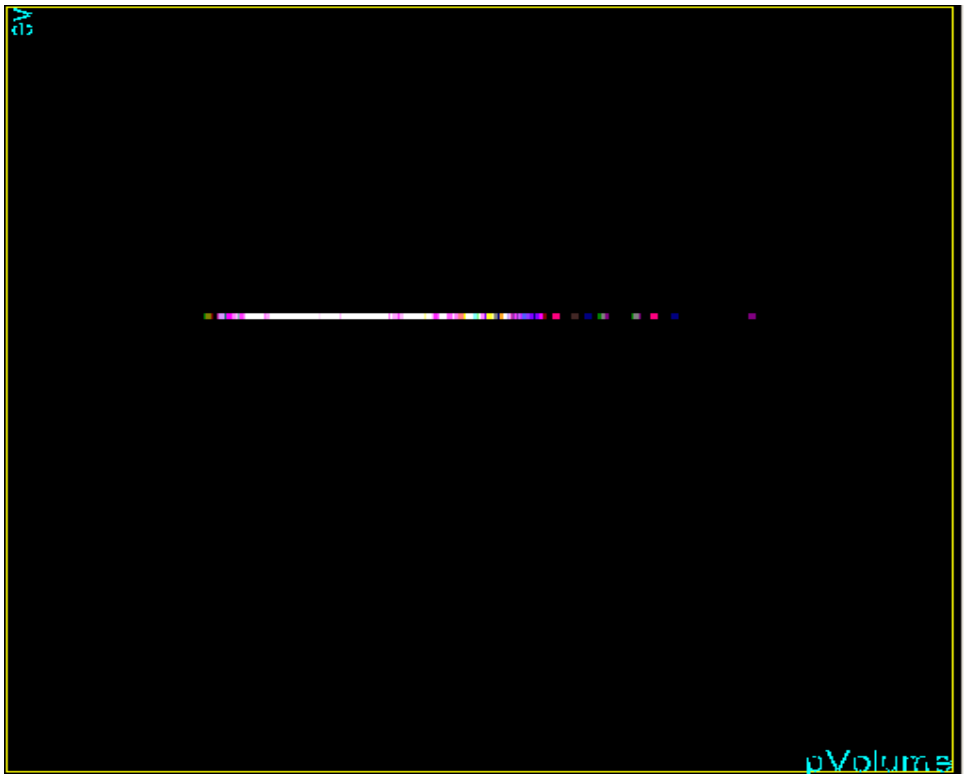

Figure 5. A scatter plot matrix of all patients successful under 3DCTGB, showing event versus initial prostate volume. The white region indicates that most successful patients had low initial prostate volume.

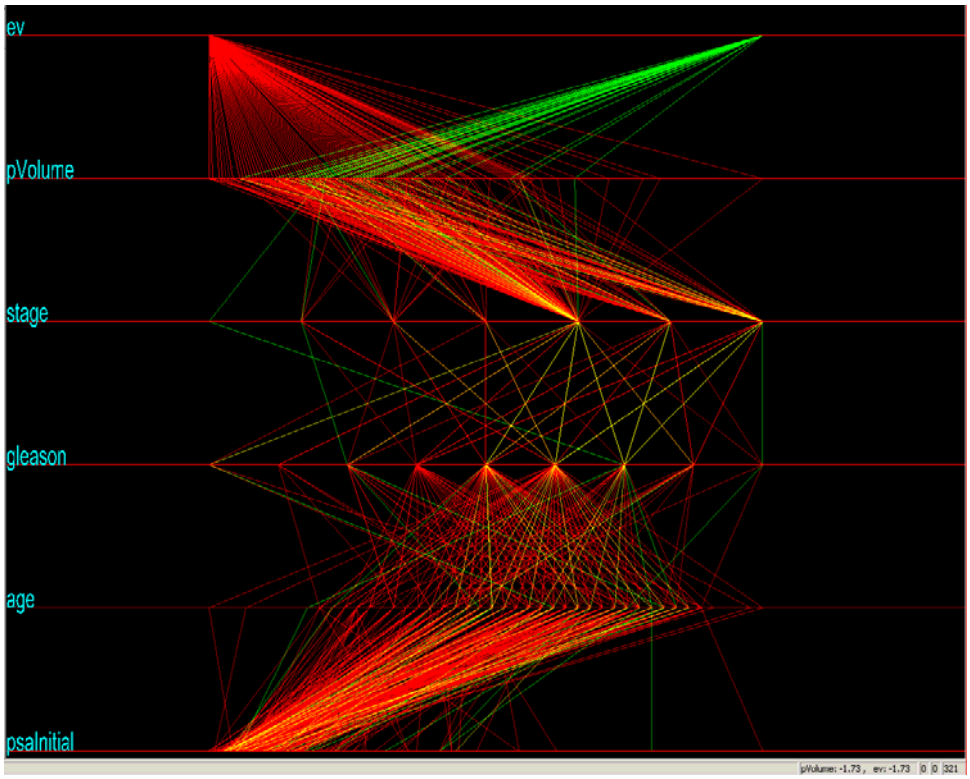

Figure 6. A parallel coordinate plot of high risk patients. Successful patients are colored in red, and patients who failed are colored in green. Note that patients who failed have both a high Gleason's score and stage. There is one outlier with respect to this inference; one patient has a low stage and high Gleason's score, but failed. Upon closer analysis, this patient's failure is a combination of a high Gleason's score and initial PSA value.

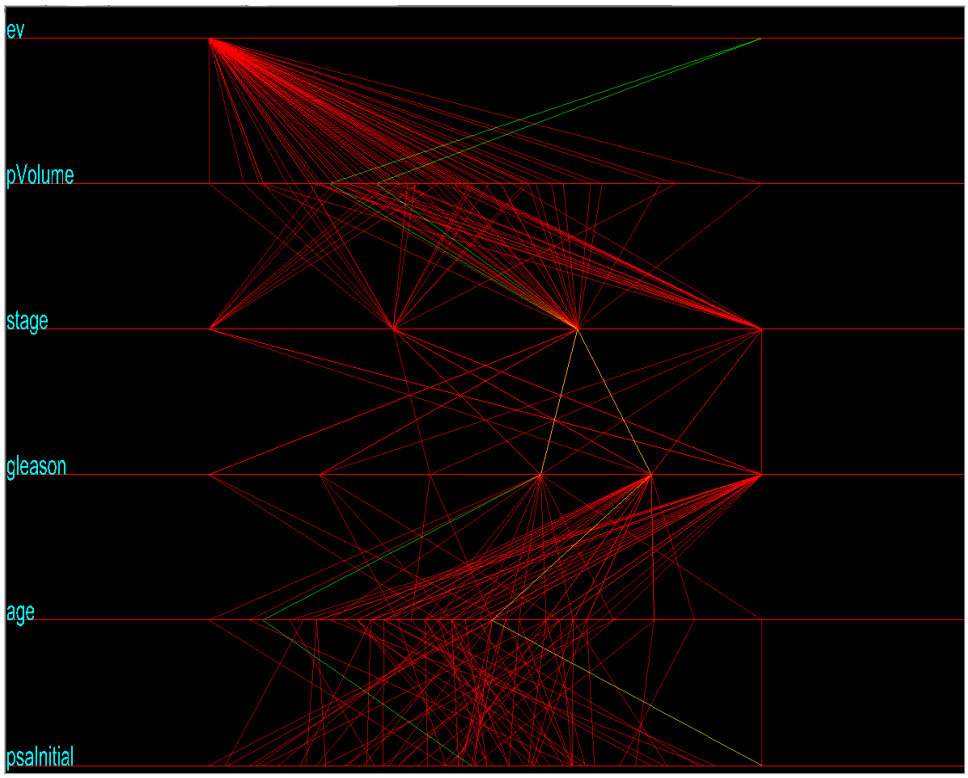

Figure 7. A parallel coordinate plot of intermediate risk patients. Successful patients are colored in red, and patients who failed are colored in green. Note that patients who failed have both a high Gleason's score and stage.

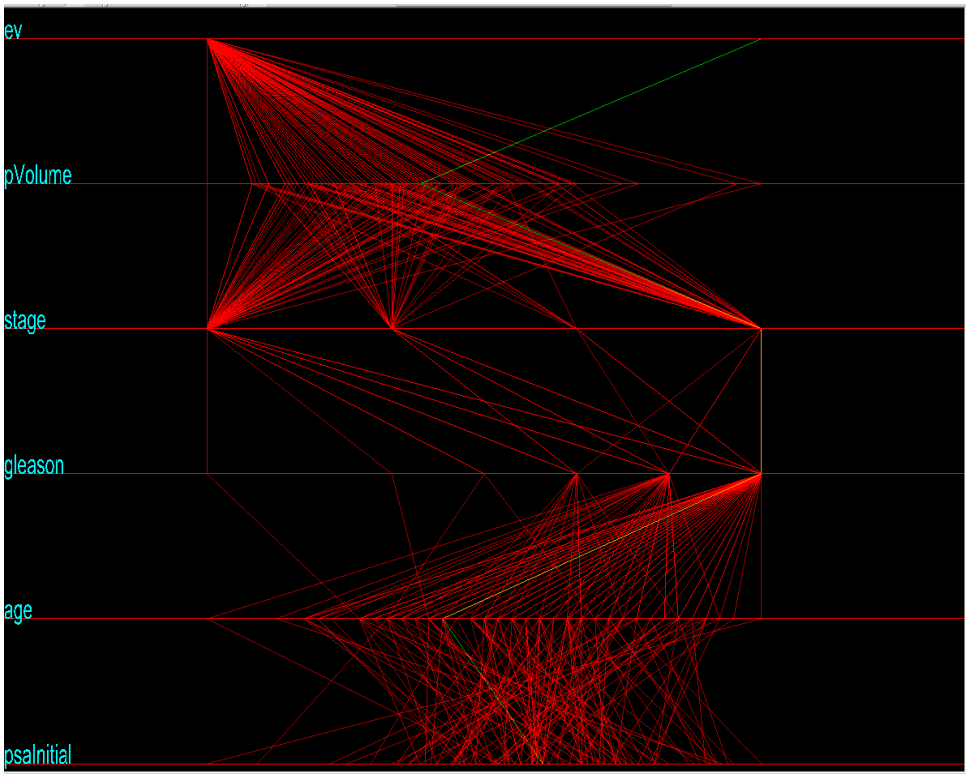

Figure 8. A parallel coordinate plot of low risk patients. Successful patients are colored in red, and patients who failed are colored in green. Note that patients who failed have both a high Gleason's score and stage. There is only one patient who failed in this group. He has a relatively high stage and Gleason's score.

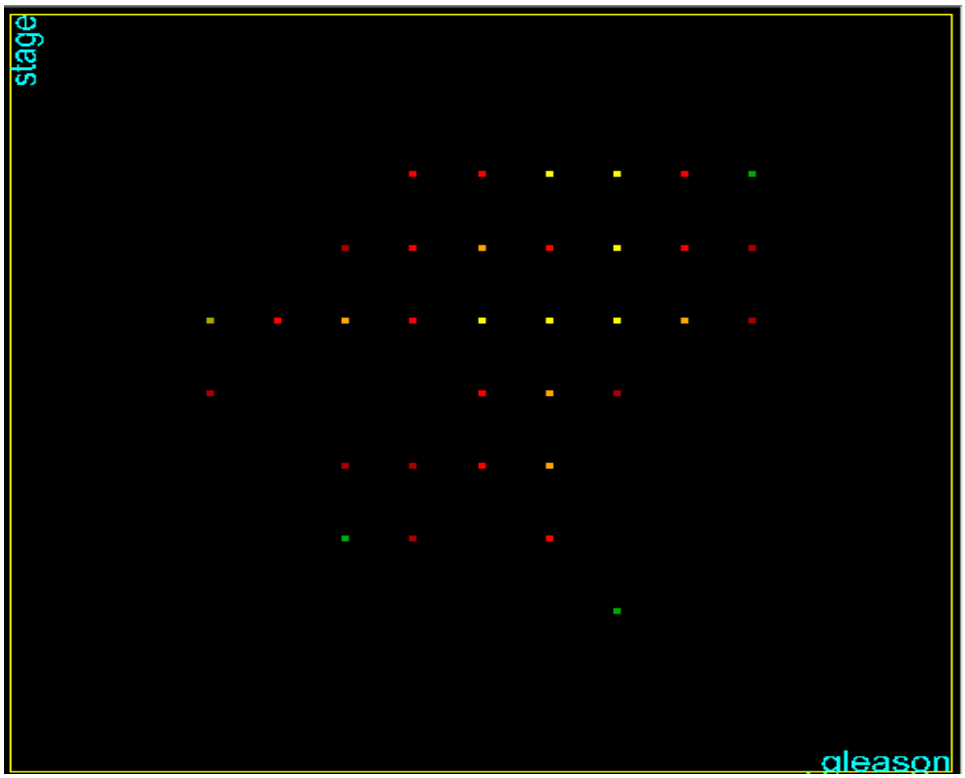

Figure 9. A scatter plot matrix of high risk patients, with the variables stage and Gleason's score. Patients who were successful are colored in red, and patients who failed are colored in green. Note that most patients who failed are found in the upper right hand corner, marked in yellow, as a result of the additive color scheme. This visualization suggests that high risk patients who failed have relatively high stage and Gleason's score. Note the green outlier of failed patients in the lower right hand corner. As stated in Figure 6, this patient failed because of a high Gleason's score and initial PSA value. Also, there is another outlier detected, using scatter plot matrix and not parallel coordinate, in the lower left hand corner. This patient had both a low Gleason's score and stage, but failed 3DCTGB. Upon closer analysis, this patient lied at the extreme of being older in age.

Table 1. Patients Characteristics Treated with 3D CT-Guided Brachytherapy June 1994 – June 2002 n 673

Characteristics	**n**	**%**
Age: Range: 42-90, Median: 68, Mean: 67 Years		
Prostate Volume < 50 cm^3	285	42%
Prostate Volume 50-59 cm^3	111	17%
Prostate Volume 60-79 cm^3	167	25%
Prostate Volume 80-100cm^3	69	10%
Prostate Volume > 100 cm^3	41	6%
Prostate Volume: Range: 14-180, Median: 54, Mean: 57.8 cm^3		
PSA < 10 ng/mL	424	63%
PSA 10-20 ng/mL	172	26%
PSA > 20 ng/mL	77	11%
PSA >= 10 ng/mL	249	37%
PSA: Range: 0-143, Median: 7.9, Mean: 11.9 ng/mL		
Gleason <= 6	432	64%
Gleason = 7	184	27%
Gleason >= 8	57	9%
Trans-Urethral Resection (1 – 3 years prior to implant)	66	10%
Post-prostatectomy Failure	9	1%
Neoadjuvant androgen ablation (3 months prior to implant)	467	69%
$Iodine^{125}$	375	56%
$Palladium^{103}$	298	44%
1997 American Joint Committee on Cancer Tumor Staging		
T1a,T1b,T1c,T2a	301	45%
T2b,T3a	312	46%
T3b (biopsy-proven SV Invasion)	60	9%

Table 2. Risk Profile and Biochemical Results of Patients Treated with 3D CT-Guided Brachytherapy 1 – 8 Years Follow-Up (median 2.3 Years) n 539

Groups	Risk Factor(s)	# Patients	bNED* %
High Risk			
3 Risks			
3a	T3b, GL >= 7, PSA 10-20 ng/mL	7	6 (86%)
3b	T3b, GL >= 7, PSA > 20 ng/mL	17	13 (76%)
3c	T2b,3a, GL >= 7, PSA 10-20 ng/mL	22	21 (95%)
3d	T2b,3a, GL >= 7, PSA > 20 ng/mL	23	20 (87%)
	Subtotal	**69**	**60 (87%)**
2 Risks			
2a	T3b, GL >= 7, PSA < 10 ng/mL	18	16 (89%)
2b	T3b, PSA 10-20 ng/mL, GL < 7	4	4 (100%)
2c	GL >= 7, PSA 10-20 ng/mL, T1a,b,c,T2a	16	15 (94%)
2d	GL >= 7, PSA > 20 ng/mL, T1a,b,c,T2a	2	1 (50%)
2e	T2b,3a, GL >= 7, PSA < 10	59	55 (93%)
2f	T2b,3a, PSA 10-20 ng/mL, GL < 7	39	35 (90%)
2g	T2b,3a, PSA > 20 ng/mL, GL < 7	15	13 (87%)
	Subtotal	**153**	**139 (91%)**
1 Risk			
1a	T3b, PSA < 10 ng/mL, GL < 7	4	4 (100%)
1b	T2b,3a, PSA < 10 ng/mL, GL < 7	82	78 (95%)
1c	PSA > 20 ng/mL, GL < 7, T1a,b,c,T2a	12	11 (92%)
1d	GL > 7, PSA < 10 ng/mL, T1a,b,c,T2a	1	0 (0%)
	Subtotal	**99**	**93 (94%)**
	High Risk Total	**321**	**292 (91%)**
Intermediate Risk			
1a	GL = 7, PSA < 10 ng/mL, T1a,b,c,T2a	25	25 (100%)
1b	PSA 10-20 ng/mL, GL < 7, T1a,b,c,T2a	49	47 (99%)
	Intermediate Risk Total	**74**	**72 (97%)**
Low Risk	PSA < 10 ng/mL, GL < 7, T1a,b,c,T2a	144	143 (99%)
	High and Intermediate Total	**539**	**507 (94%)**

***Biochemical no evidence of disease.**

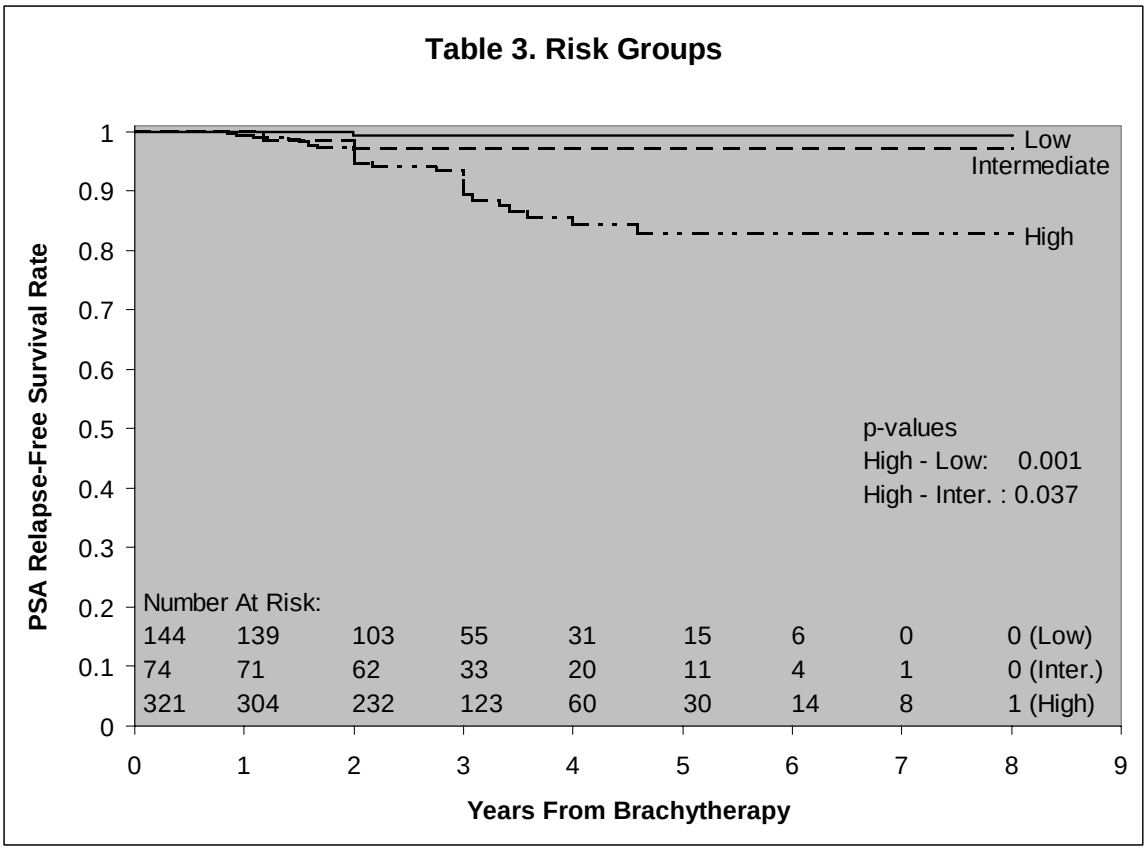
Table 3. Risk Groups
PSA Relapse-Free Survival Rate
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Low
Intermediate
High
p-values
High - Low: 0.001
High - Inter. : 0.037
Number At Risk:
144 139 103 55 31 15 6 0 0 (Low)
74 71 62 33 20 11 4 1 0 (Inter.)
321 304 232 123 60 30 14 8 1 (High)
0 1 2 3 4 5 6 7 8 9
Years From Brachytherapy

References

1. ASTRO Consensus Panel. (1997) "Consensus statement: Guidelines for PSA following radiation therapy." Int. J. Radiat. Oncol. Biol. Phys. Vol (37), pp 1035-1041.
2. Inselberg, Alfred. (1985), "The plane with parallel coordinates." The Visual Computer vol (1), pp 69 – 91.
3. Inselberg, Alfred. (2002) "Visualization and data mining of high-dimensional data." Chemometrics and Intelligent Laboratory Systems, vol (60), pp 147 – 159.
4. Koutrouvelis, PG. (1998) "Three-dimensional stereotactic posterior ischiorectal space computerized tomography guided brachytherapy of prostate cancer: a preliminary report." J Urol, vol (159), pp 142-145.
5. Prostate Cancer. [Online], (2003), University of Michigan Comprehensive Cancer Center. Available: http://www.cancer.med.umich.edu/prostcan/prosintro.htm (April 20, 2003).
6. Van Halteren, H.K. "Colorectal cancer in 2003: old principles, new strategies." Anti-Cancer Drugs. Vol. (14, 2), pp 97–102.
7. Wegman, E.J., and Dorfman, A. (2003), "Visualizing cereal world." Computational Statistics & Data Analysis, vol (43, 4), pp: 633-649.