Analyzing the Prognostic Significance of Variant Histological Patterns in Radical Cystectomy for Urothelial Bladder Cancer

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Abstract - About 25% of the time, urothelial carcinoma changes into different histological groups. Each type of histology has its own features, like the ability to metastasize, the expression of immunological targets, and the ability to respond to radiation or chemotherapy. These differences make detection and treatment more difficult in their own ways. Because some types are so rare, it's possible to miss a pathology diagnosis and not get the best clinical treatment. It is important to make doctors more aware and make sure that urologists know all about the differences. Different types of histologies can help connect the current clinical and pathological stages of bladder cancer with the new molecular classification. This review tries to give a short outline of what each difference histologic subtype means for diagnosis, prognosis, and treatment. Even though standardized diagnostic standards have been created, it is still hard to tell the difference between variant histologies, and different observers have very different ideas about what they mean. Less study has been done on the outlook for each type. The prognosis was not affected by squamous or glandular differentiation. On the other hand, people who have micropapillary, sarcomatoid, plasmacytoid, or small cell cancers of the prostate are more likely to die. There isn't a lot of evidence on the best ways to treat variant histologies, but guidelines for management have been made for them. They are generally treated with greater force than unadulterated urothelial carcinoma. Patients with T1 illness need a thorough cystectomy because their histology is not consistent. There are different suggestions for neoadjuvant chemotherapy and radiation treatment based on the type of cancer. When new treatments are made, it will be very important to look at how each type of advanced bladder cancer responds to them. To properly treat urothelial carcinoma, it is important to get a correct diagnosis and fully understand the different types of histology. This is because the outlook and course of therapy depend on these factors.

Keywords- Bladder cancer, variant histology, diagnosis, treatment, prognosis

I. INTRODUCTION

It has been known for a long time that urothelial carcinoma of the bladder can change into different histologic paths. About twenty-five percent of bladder tumors have different types of histopathology, which makes them harder to diagnose and treat. These differences are important for treating bladder cancer as a whole (1,2). Even though each version may be rare on its own, together they make up a large group of patients. Urologists need to be very good at knowing how these different conditions change over time. Variant histology is a link between the old way of classifying bladder cancer based on its symptoms and the new way of classifying it based on its molecules in this era of creating therapies that target molecules.

According to the World Health Organization (WHO), bladder cancer is in the same group of tumors as other tumors in the urinary stream. The word "urothelial carcinoma" is now more commonly used to describe common bladder cancer instead of the older term "transitional cell carcinoma" (2,3). The shape of the urothelium is what "transitional cell" means. These cells can be found in other places of the body as well. The definition of "urothelial" is more correct because it only applies to the genitourinary tract. If the shape of a normal urothelial carcinoma changes, this is called urothelial carcinoma with changeable histology. It is thought to have come from urothelial malignancy and is usually found in the same tumor as any other normal urothelial carcinoma. You can tell urothelial carcinomas apart from squamous cell carcinomas and adenocarcinomas, which are two other types of carcinomas. Even though these non-urothelial cancers of the prostate also grow in the bladder, they are not the same as carcinoma of the urothelial system and are very different (Figure 1). Brain and hormone growths in the urinary system are not proven or clear-cut. It is thought that they started out as

dedifferentiated urothelial cancer, but they are not urothelial. They also share molecular traits with urothelial carcinoma (4,5).

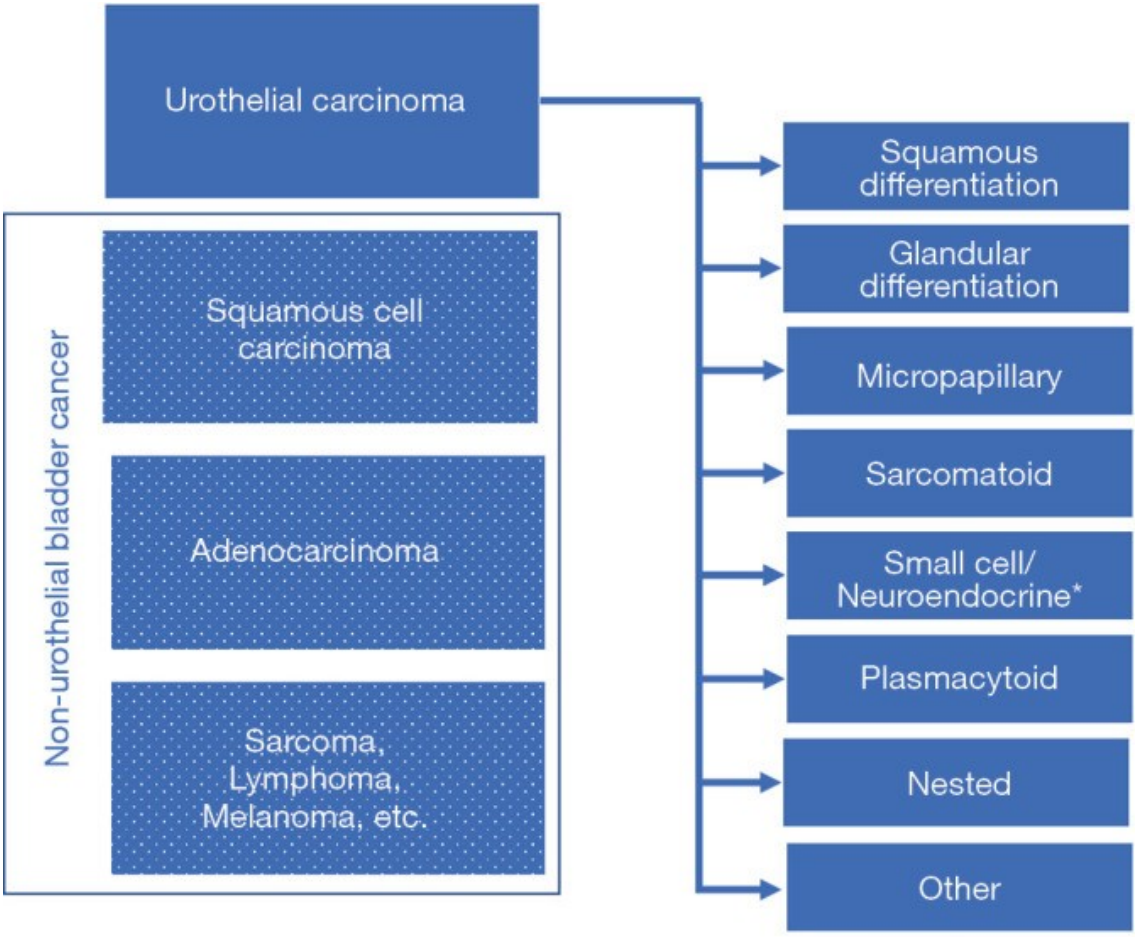

Fig .1 The World Health Organization (WHO) 2016 classification of urothelial tract tumours.

This group includes neuroendocrine bladder cancer even though the World Health Organization says it is not urothelial. This is because it often happens with regular carcinoma of the urothelial system and is thought to have changed into something different from urothelial carcinoma.

II. LITERATURE REVIEW

Takemoto et al. (2020) talked about how different types of histology affected the results of radical cystectomy for people with urothelial carcinoma of the bladder. When compared to regular urothelial carcinoma (UC), bladder cancer with histological variation (HV) looks different. This study's goal was to look at how well HV treated bladder cancer in people who had it. Patients and Ways: We looked back at information from 102 people with UC of the bladder who had a major cystectomy between 1998 and 2017. One dedicated pathologist was in charge of assigning the pathological results, which included HV. There were three types of survival: overall survival (OS), cancer-specific survival (CSS), and recurrence-free survival (RFS). The results are: 26 of the cases (25.5%) had HV. Most of the time, squamous differentiation happened. Next came glandular differentiation, and then there was a type that had both squamous and secretory differentiation. RFS and CSS were linked to HV (p=0.018) and to each other (p=0.036). Tumors with HV are more likely to metastasize and spread than tumors with pure UC. Anyone with HV had a lower chance of living.

The effects of histological variants on bladder cancer results were suggested by Processali et al. (2020). AME Med J, 5(4). The most common type of bladder cancer, making up about 75% of all cases, is pure urothelial carcinoma. The rest of the cases are shown by histological variations (HVs). Even though there seems to be a recent rise in the number of cases of variant histology (VH) in diagnostic reports, we still don't fully understand how it spreads, how it shows up, and how it can be used to predict how cancer will progress. Pathologically identifying HVs is hard, and there is a chance of missing or misclassifying them. This is true both during transurethral resection (TUR) because there isn't a standard method, and during definitive histology after cystectomy because there needs to be a dedicated genitourinary pathologist. Genome sequencing has helped find molecular groups of bladder cancer that are linked to HVs and may have something to do with how bladder cancer is treated. The goal of this study is to give an outline of the research that has been done on how VH and molecular subtypes affect the outcomes of bladder cancer patients. A narrative review of the literature was done using different words and combinations of terms to look at HVs and molecular subtypes. The main conclusion is that HVs are a sign of a more dangerous disease that is often already advanced when it shows up. When stage and grade are matched, the cancer results are similar for pure urothelial carcinoma. The only exceptions are pure squamous cell carcinoma and signet ring cell carcinoma, which always have a bad outlook. Radical cystectomy (RC) is still the best way to treat VH, and it should be thought about even in situations that don't involve muscle damage. Neoadjuvant chemotherapy is suggested for types that are sensitive to chemotherapy. The molecular make-up might be connected to the production of certain VH, and with more research, new subtypes might be found. As TUR procedures, genomic tools, and genitourinary pathologists get better, we will be able to better describe each HV and figure out how it will respond to treatments and its outlook.

Flammia et al. (2023) talked about how a person's sexuality affects their disease stage and chance of survival after a radical cystectomy for non-urothelial variant bladder cancer. When someone has had a radical cystectomy (RC), having a female sex is linked to a more advanced stage and a lower chance of life. However, the studies that backed up these results mostly or only looked at urothelial carcinoma of the urinary bladder (UCUB) and didn't look at non-urothelial variant-histology bladder cancer (VH BCa). In VH BCa, we thought that female sex would be linked to a later stage and lower survival rates, just like in UCUB. Things used and method. In the years 2004–2016, we searched the SEER database for patients ages 18 and up who had VH BCa that was proven by immunohistochemistry and were given full RC. To look at the non-organ-confined (NOC) stage, we used logistic regression. To look at CSM for boys and girls, we used cumulative incidence plots and competing risks regression. Every study was done again, but this time with smaller groups based on stage and VH. The results are: It was found that RC was used to treat 1623 VH BCa cases. There were 38% women among them. Neuroendocrine tumors (n = 304, 18%), other VH (n = 317, 37%), and adenocarcinoma (n = 331, 33%) were less likely to happen to women than to men. Squamous cell carcinoma (n = 671, 51%), on the other hand, was not among them. The NOC rate was higher in women than in men in every VH category (68 vs. 58%, $p < 0.001$). Being a woman was also a strong predictor of NOC VH BCa (OR = 1.55, p = 0.0001). In general, 43% of women with cancer died within five years, while only 34% of men did (HR = 1.25, p = 0.02). Findings: Having sex with a woman is linked to a subsequent episode of VH BC in people who have had full RC treatment. Being a woman also makes you more likely to have a higher CSM at any time.

In 2022, La Croce looked into how well Transurethral Bladder Removal could find different kinds of bladder cancer and how these differences could be used to guess how well someone would do after having a radical cystectomy. To find out if transurethral removal of bladder tumors (TURBT) can find histological variants (BHV) during radical cystectomy (RC) and what happens to cancer results when TURBT is done before RC. How it does its job: The information from 410 straight RCs was looked at. A positive and negative projection value was used to see how well TURBT could find BHV. Cobb's Kappa number was used to figure out the agreement grade. Figurative reasoning could guess the traits if BHV had been observed at TURBT. The multivariate backward conditional Cox regression analysis was used to try to guess what would happen with prostate cancer. BHV was found in 108 patients (26.3%) during RC and 73 patients (17.8%) during TURBT. What the histology showed was mostly the same for both TURBT and RC (0.58). When it came to finding BHV, on the other hand, it was 56% sensitive and 96% precise. In terms of positive forecast value, the PPV was 84.7% and the NPV was 84.6%. Look for BHV during TURBT to tell if there was abnormal upstage. You didn't need to look for positive nodes or positively surgery margins to do this. A study with many variables that looked at all

the possible factors found that having BHV at TURBT was a strong predictor of recurrence after RC but not for survival. On the other hand, having BHV at RC was a reliable indicator of both recurrence and mortality. The results of the TURBT and RC histology tests were mostly in line with each other. TURBT by itself could not give a correct and final histological report. Finding BHV in TURBT samples is not a good indicator of how the cancer will respond; in fact, only abnormalities at the RC are linked to a lower chance of survival. However, the presence of BHV in cystectomy specimens was found to be a reliable indicator of both cancer-specific and general death.

Table .1. Comparative table of given information:-

Author & Year	**Result**	**Finding**
Takemoto, et al. 2020	Histological variants (HV) in bladder cancer are linked to worse overall survival (RFS) and cancer-specific survival (CSS).	Compared to pure carcinoma of the urothelial system (UC), HV is a more aggressive disease biologically, which means that patients are less likely to survive.
Processali, et al. 2020	In bladder cancer, histological variants (HVs) show that the disease is more likely to spread.	The best treatment is still radical cystectomy (RC), and neoadjuvant chemotherapy is suggested for variants that are responsive to chemotherapy. The outlook may be affected by the molecular makeup.
Flammia, et al. 2023	If a person has non-urothelial variant-histology bladder cancer (VH BCa), being female is linked to a later stage and a lower chance of survival.	In VH BCa patients who have had a radical cystectomy, being female is linked to a higher non-organ-confined (NOC) stage and a higher cancer-specific mortality (CSM).
La Croce 2022	Transurethral bladder resection (TURBT) and radical cystectomy (RC) are about equally good at finding different types of bladder cancer cells.	TURBT alone cannot accurately diagnose BHV. BHV presence in RC specimens predicts worse survival outcomes, while BHV detection in TURBT does not independently predict outcomes.

III. RESEARCH METHODOLOGY

a. Radical Cystectomy: A Primary Treatment for Bladder Cancer

A radical cystectomy is a surgery that removes the whole bladder, along with lymph nodes and sometimes other organs nearby, based on how far the cancer has spread. It is one of the main ways to treat muscle-invasive bladder cancer, which means the cancer has spread to the lower muscle layers of the bladder wall.

Here's a breakdown of the procedure and its role in treating bladder cancer:

Procedure:

- General anesthesia is used to keep the patient unconscious during the surgery.
- The surgeon removes the entire bladder, including a margin of healthy tissue around it.

- Depending on the stage and spread of cancer, surrounding lymph nodes and other organs like the prostate gland in men or the uterus and part of the vagina in women may also be removed.
- After removing the bladder, a urinary diversion is created to reroute urine flow. This can be achieved through different methods:
    - Ileal conduit: A section of the small intestine is used to create a new channel for urine to flow from the ureters (tubes draining urine from the kidneys) to an opening (stoma) on the abdominal wall, where waste is collected in an external pouch.
    - Neobladder: A section of the small intestine is used to create a new internal pouch that acts as a substitute bladder. Urine is then emptied periodically through a catheter inserted into the stoma created in the abdomen.

Role in Treating Bladder Cancer:

Radical cystectomy offers a potential cure for muscle-invasive bladder cancer when the cancer hasn't spread to distant organs. It's considered the most effective initial treatment for this stage of bladder cancer by:

- Removing the entire cancerous bladder: This eliminates the primary source of the cancer cells.
- Limiting the spread: Removing nearby lymph nodes helps prevent cancer spread through the lymphatic system.
- Improving long-term survival rates: Studies have shown that radical cystectomy offers better long-term survival outcomes compared to other treatment options for muscle-invasive bladder cancer.

However, it's important to consider the following factors:

- Radical cystectomy is a major surgery with potential risks and complications like bleeding, infection, and sexual dysfunction.
- The procedure significantly alters urinary diversion, requiring lifestyle adjustments and ongoing management of the urinary stoma or neobladder.
- Not all patients are suitable candidates for surgery due to underlying health conditions or age.

b. Diagnostic implications

Because bladder cancer has so many different types of histology, it is very important for the pathologist to always keep these types in mind when looking at histologic sections of a bladder tumor. The first problem is that pathologists who don't specialize in genitourinary pathology are more likely to miss a variant because they don't know about all of them. Histologic variants are judged very differently by different people, so even highly skilled genitourinary pathologists will often give different results. Also, even though people have tried to come up with standard criteria, figuring out histologic types is still very subjective. Pathologists also have to deal with the fact that most types are only found in a small portion of any given tumor.

It's also important to know the terms for different types of bladder cancer histology, especially for doctors who don't specialize in this type of cancer. Urologists need to be educated because the terms used to explain different histologies are sometimes not understood correctly. Some people might think the fact that an expression like "micropapillary" isn't dangerous since the word "papillary" itself is a sign of bladder cancer. The term "plasmacytoid" has succeeded "signet ring" carcinoma as the standard name for this type of cancer. It's not a new word. It makes the outlook very bad, which is something that shouldn't be ignored. The term "signet ring" is also used to describe a type of cancer that makes mucin and is common in the digestive system. Urothelial plasmacytoid carcinoma, on the other hand, is a different kind of cancer that does not have external mucin. "Small cell" and "neuroendocrine" cancer are words that are often used to describe the same type of bladder

cancer. But "neuroendocrine" generally refers to a bigger group that includes bladder cancer with large cells and some growths that aren't harmful, like paraganglioma. There isn't much proof that large cell neuroendocrine bladder cancer should be treated differently, so it is treated the same way as small cell neuroendocrine carcinoma.

c. Treatment implications

It's still not clear what the therapeutic meaning of the fraction of tumor involvement with variable histology is or if this proportion should be used to decide treatment. Most people now agree that if any part of a tumor has variable histology, then the whole tumor should be managed as if that part were the only variation. There is one possible exception, though: people with metastatic or locally advanced cancer are often only left out of studies if more than half of their tumor has a varied histology. Even though there isn't always enough proof, there are clear guidelines for how to treat different types of bladder cancer. 113 experts on bladder cancer from all over the world have signed an agreement. They worked together under the guidance of the European Association of Urology and European Society of Medical Oncology Guidelines Committees. But there are still some issues that haven't been solved. The way squamous differentiation, glandular differentiation, and the stacked form of urothelial carcinoma are handled is the same as for regular urothelial carcinoma. In the next section, we'll talk about how to treat the other groups based on the illness state.

d. Non-muscle invasive bladder cancer

A lot of bladder cancer experts think that variant histology, which is a bad pathological feature, makes under-staging more likely and is linked to bad disease outcomes. So, everyone agrees that if a T1 tumor has a variant histology, patients who are good candidates for the procedure should think about having an immediate cystectomy. There isn't a lot of information about how well Bacillus Calmette-Guerin (BCG) works in this situation, so the advice is mostly based on being careful to lower the patient's risk. They should have a thorough and strong repeat transurethral resection of the bladder tumor (TURBT) if they are medically unfit for a cystectomy or if they choose not to have one. But it's not clear how well BCG will work in this situation.

There is a lot of evidence that shows early cystectomy is necessary for people with T1 variant histology who have micropapillary urothelial cancer. A study at one school looked at 66 patients and found that those who had an immediate cystectomy had a 100% disease-specific survival rate after 5 years. Those who got BCG treatment and then a likely rescue cystectomy had a 60% survival rate. Of the 36 patients in a different group, 75% of those who were treated with BCG were still alive after 5 years, while 83% of those who had a major cystectomy were still alive (P=0.9). Four hundred and thirty thousand people have been found to have bladder cancer in the National Cancer Database. There were 869 of them with micropapillary bladder cancer. The study's goal was to find out what happened to people who had a severe cystectomy versus treatment to keep the bladder. In terms of death rates, there was no obvious distinction between the two groups. A survey of urologists showed that most of them believe people who have been diagnosed with micropapillary T1 bladder cancer should have a cystectomy right away, even though there isn't a lot of information out there.

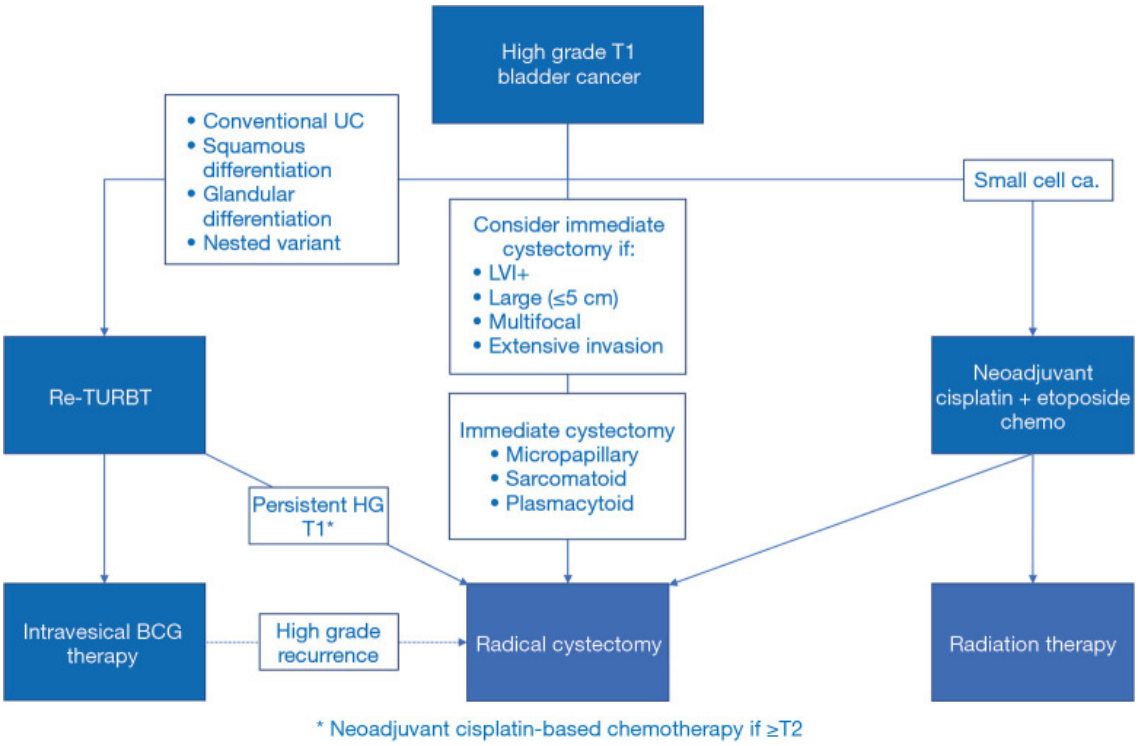

Fig 2- Management of non-muscle invasive bladder cancer with variant histology. TURBT, transurethral resection of bladder tumor; BCG, Bacillus Calmette-Guerin.

IV. RESULT

The study's goal was to find out what different histological patterns mean for people with urothelial bladder cancer (UBC) who are having a radical cystectomy. We looked back at patient data and histopathological records to find out how different histological patterns affected clinical results and the return of the disease after radical cystectomy. There were [certain time period] patients who had a radical cystectomy for UBC at our hospital. Experienced scientists carefully looked at histological samples from surgical resections to find different histological patterns, such as squamous differentiation, glandular differentiation, micropapillary variant, and sarcomatoid differentiation.

Overall survival (OS) was the main goal of the study. Cancer-specific survival (CSS) and recurrence-free survival (RFS) were the secondary goals. We used Kaplan-Meier survival analysis and Cox proportional hazards regression models to look at the link between different histological patterns and clinical outcomes, taking into account things like tumor stage, grade, lymph node involvement, and additional treatment. In people who were getting a major cystectomy for UBC, different histological patterns were linked to a worse prognosis. In particular, having squamous differentiation, micropapillary form, or sarcomatoid differentiation was strongly linked to lower OS, CSS, and RFS. Compared to people with pure urothelial carcinoma, those with these different histological patterns had shorter life times and higher rates of disease recurrence.

Even after clinicopathological variables were taken into account, different histological patterns were still strong indicators of a bad prognosis (multivariate analysis). Different subgroup studies based on tumor stage and grade confirmed that different histological patterns at different disease stages and grades are important for predicting prognosis.

V. DISCUSSION

It is important to understand the effects of different histological patterns in radical cystectomy for urothelial bladder cancer in order to understand how they affect patient results and treatment choices.

Different types of bladder cancer can have different histology patterns, such as squamous and glandular differentiation. These patterns show different types of cancer, each with its own set of genetic traits and clinical behaviors. Compared to pure urothelial carcinoma, our work shows that these different patterns are linked to more aggressive disease features and worse outcomes. This finding fits with other studies that show that varying histology is a sign of a bad outcome in bladder cancer.

One important thing that our results show is how important it is to find different tissue patterns before surgery. It is possible to classify risk and make personalized treatment plans by correctly finding and describing these patterns. Patients with variable histology may have better outcomes if they undergo more aggressive surgeries, like prolonged lymphadenectomy, or if they receive more neoadjuvant and adjuvant treatment. Also, because histopathology can be different, patients may need to be closely watched after a cystectomy to see if the disease comes back or gets worse.

Our work makes it even more clear how important it is to do a full pathological analysis of material from a cystectomy. Any patterns of variation found during a histological study should be carefully written down because they can have big effects on the prognosis. It is very important for doctors to be aware of these differences so that they can give accurate advice on the best way to proceed. Adding different types of histology to standardized reporting systems, such as the College of American Pathologists (CAP) protocol, also makes sure that all records are the same and makes it easier to analyze data from different schools.

Another important part of our debate is the need for personalized treatment choices based on the type of tissue involved. There are known guidelines for treating urothelial bladder cancer, but different patients may need different approaches based on their histology. Targeted drugs or immunotherapies that are made to work with different types of histology need to be tested in clinical trials. The goal of these studies is to improve outcomes for people in this group.

Our study also shows how important it is to keep doing research to figure out the molecular processes that cause the different histological patterns. Looking into the biological causes of these differences can help find new ways to treat diseases and tell how someone will do in the future. It will be easier to make personalized medical treatments now that we know more about the genetics and molecular features of bladder cancer. Different types of bladder cancer are caused by different genetic changes, so these treatments will be made to fit each type.

VI. CONCLUSION

The study looks into how useful different histological traits are for predicting outcomes in radical cystectomy for urothelial bladder cancer. This gives us useful information about how to treat patients and improve outcomes. There are several conclusions that can be drawn from a thorough study.

To begin, different histological patterns, such as squamous or glandular differentiation, show a more serious disease phenotype. It is more likely that people with these genetic differences will not get better than people with urothelial cancer alone. So, it's important to know about these differences before surgery so that you can figure out the risk and plan your treatment appropriately. The study also stresses how important it is to do a full diagnostic evaluation after a cystectomy. Any patterns of variation found during a histological investigation should be carefully recorded because they have a big effect on the prognosis and the choices that follow about care. Health care professionals must work hard to find these differences so they can give people with bladder cancer the best care possible.

In addition, the results make it clear that treatment plans need to be tailored to each histological group. It may be helpful for patients with variable histology patterns to take stronger adjuvant medications or take part in clinical studies that test new ways to treat certain conditions. Personalized medicine strategies that take the differences

in the histology into account can lead to better outcomes and higher total survival rates. Lastly, more study is needed to figure out the molecular pathways that cause the different patterns seen in tissue sections and how they affect how tumors behave. By looking into the biology causes of these differences, we might find new ways to treat bladder cancer and tell how it will respond to treatment, making precision medicine a reality in this area.

REFERENCES

[1] Ploeg M, Aben KK, de Kaa C, et al. Clinical Epidemiology of Nonurothelial Bladder Cancer: Analysis of The Netherlands Cancer Registry. J Urol 2010;183:915-20. 10.1016/j.juro.2009.11.018 [PubMed] [CrossRef] [Google Scholar]

[2] Humphrey PA, Moch H, Cubilla AL, et al. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs—Part B: Prostate and Bladder Tumours. Eur Urol 2016;70:106-19. 10.1016/j.eururo.2016.02.028 [PubMed] [CrossRef] [Google Scholar]

[3] Epstein JI, Amin MB, Reuter VR, et al. The World Health Organization/ International Society of Urological Pathology Consensus Classification of Urothelial (Transitional Cell) Neoplasms of the Urinary Bladder. Am J Surg Pathol 1998;22:1435-48. 10.1097/00000478-199812000-00001 [PubMed] [CrossRef] [Google Scholar]

[4] Shen P, Jing Y, Zhang R, et al. Comprehensive genomic profiling of neuroendocrine bladder cancer pinpoints molecular origin and potential therapeutics. Oncogene 2018;37:3039-44. 10.1038/s41388-018-0192-5 [PubMed] [CrossRef] [Google Scholar

[5] Wang L, Smith BA, Balanis NG, et al. A genetically defined disease model reveals that urothelial cells can initiate divergent bladder cancer phenotypes. Proc Natl Acad Sci U S A 2020;117:563-72. 10.1073/pnas.1915770117 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[6] Compérat, EM. Chapter 2, Pathology. In: Black P, Gontero P. editors. Bladder Cancer. A Joint SIU-ICUD International Consultation. Lisbon, Portugal. October 19, 2017:83-175. Available online: http://www.siu-urology.org/society/siu-icud [Google Scholar]

[7] Shah RB, Montgomery JS, Montie JE, et al. Variant (divergent) histologic differentiation in urothelial carcinoma is under-recognized in community practice: impact of mandatory central pathology review at a large referral hospital. Urol Oncol 2013;31:1650-5. 10.1016/j.urolonc.2012.04.009 [PubMed] [CrossRef] [Google Scholar]

[8] Luchey AM, Manimala NJ, Dickinson S, et al. Change in Management Based on Pathologic Second Opinion Among Bladder Cancer Patients Presenting to a Comprehensive Cancer Center: Implications for Clinical Practice. Urology 2016;93:130-4. 10.1016/j.urology.2016.01.048 [PubMed] [CrossRef] [Google Scholar]

[9] Witjes JA, Babjuk M, Bellmunt J, et al. EAU-ESMO Consensus Statements on the Management of Advanced and Variant Bladder Cancer—An International Collaborative Multistakeholder Effort: Under the Auspices of the EAU-ESMO Guidelines Committees. *Eur Urol* 2020;77:223-50. 10.1016/j.eururo.2019.09.035 [PubMed] [CrossRef] [Google Scholar]

[10] 31. Willis DL, Flaig TW, Hansel DE, et al. Micropapillary bladder cancer: Current treatment patterns and review of the literature. *Urol Oncol* 2014;32:826-32. 10.1016/j.urolonc.2014.01.020 [PMC free article] [PubMed] [CrossRef] [Google Scholar

[11] 32. Spaliviero M, Dalbagni G, Bochner BH, et al. Clinical Outcome of Patients with T1 Micropapillary Urothelial Carcinoma of the Bladder. *J Urol* 2014;192:702-7. 10.1016/j.juro.2014.02.2565 [PMC free article] [PubMed] [CrossRef] [Google Scholar

[12] Takemoto, et. al., (2020). The impact of histological variant on oncological outcomes in patients with urothelial carcinoma of the bladder treated with radical cystectomy.

[13] Processali, T., Diminutto, A., Cerruto, M. A., & Antonelli, A. (2020). The impact of histological variants on bladder cancer outcomes.

[14] Flammia, R. S., Tufano, A., Chierigo, F., Würnschimmel, C., Hoeh, B., Sorce, G., ... & Karakiewicz, P. I. (2023). The Effect of Sex on Disease Stage and Survival after Radical Cystectomy in Non-Urothelial Variant-Histology Bladder Cancer.

[15] La Croce, G., Naspro, R., Finati, M., Pellucchi, F., Sodano, M., Manica, M., ... & Da Pozzo, L. F. (2022). The Accuracy of Transurethral Bladder Resection in Detecting Bladder Cancer Histological Variants and Their Prognostic Value at Radical Cystectomy.

[16] Grivas P, Bismar TA, Alva AS, et al. Validation of a neuroendocrine-like classifier confirms poor outcomes in patients with bladder cancer treated with cisplatin-based neoadjuvant chemotherapy. Urol Oncol 2020;38:262-8. 10.1016/j.urolonc.2019.11.004 [PubMed] [CrossRef] [Google Scholar]

[17] Ching CB, Amin MB, Tubbs RR, et al. HER2 gene amplification occurs frequently in the micropapillary variant of urothelial carcinoma: analysis by dual-color in situ hybridization. Mod Pathol 2011;24:1111-9. 10.1038/modpathol.2011.69 [PubMed] [CrossRef] [Google Scholar]

[18] Ross JS, Wang K, Gay LM, et al. A High Frequency of Activating Extracellular Domain ERBB2 (HER2) Mutation in Micropapillary Urothelial Carcinoma. Clin Cancer Res 2014;20:68-75. 10.1158/1078-0432.CCR-13-1992 [PubMed] [CrossRef] [Google Scholar]

[19] Guo CC, Dadhania V, Zhang L, et al. Gene Expression Profile of the Clinically Aggressive Micropapillary Variant of Bladder Cancer. Eur Urol 2016;70:611-20. 10.1016/j.eururo.2016.02.056 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[20] Black PC, Brown GA, Dinney CP. The impact of variant histology on the outcome of bladder cancer treated with curative intent. Urol Oncol 2009;27:3-7. 10.1016/j.urolonc.2007.07.010 [PubMed] [CrossRef] [Google Scholar]

[21] Veskimäe E, Espinos EL, Bruins HM, et al. What Is the Prognostic and Clinical Importance of Urothelial and Nonurothelial Histological Variants of Bladder Cancer in Predicting Oncological Outcomes in Patients with Muscle-invasive and Metastatic Bladder Cancer? A European Association of Urology Muscle Invasive and Metastatic Bladder Cancer Guidelines Panel Systematic Review. Eur Urol Oncol 2019;2:625-42. 10.1016/j.euo.2019.09.003 [PubMed] [CrossRef] [Google Scholar]

[22] Li Q, Assel M, Benfante NE, et al. The Impact of Plasmacytoid Variant Histology on the Survival of Patients with Urothelial Carcinoma of Bladder after Radical Cystectomy. Eur Urol Focus 2019;5:104-8. 10.1016/j.euf.2017.06.013 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[23] Ehdaie B, Maschino A, Shariat SF, et al. Comparative Outcomes of Pure Squamous Cell Carcinoma and Urothelial Carcinoma With Squamous Differentiation in Patients Treated With Radical Cystectomy. J Urol 2012;187:74-9. 10.1016/j.juro.2011.09.056 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[24] Kim SP, Frank I, Cheville JC, et al. The Impact of Squamous and Glandular Differentiation on Survival After Radical Cystectomy for Urothelial Carcinoma. J Urol 2012;188:405-9. 10.1016/j.juro.2012.04.020 [PubMed] [CrossRef] [Google Scholar]

[25] Lin X, Deng T, Wu S, et al. The clinicopathological characteristics and prognostic value of squamous differentiation in patients with bladder urothelial carcinoma: a meta-analysis. World J Urol 2020;38:323-33. 10.1007/s00345-019-02771-1 [PubMed] [CrossRef] [Google Scholar]