TNMF versus TNM in staging of colorectal cancer

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Emeritus Professor of G. & CR surgery Cairo university

Introduction:

- Classification (TNM) staging and histologic grading of rectal cancer has undergone no or minimal changes during the past 30 years despite their major impact on planning, reporting and outcome of the disease.

- The addition of a letter (F) (for prognostic risk factors either microscopic or macroscopic) to the TNM as TNM‘F’ would theoretically warn the treating physician of the need to give adjuvant treatment in otherwise early stages and in apparently low grades of the disease.

EDITORIAL

Outcome Prediction in Rectal Cancer Beyond the Current TNM System—An Unmet Need

Manuel Rodriguez-Justo, M.D., F.R.C.Path.[1,2]

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- Despite its worldwide use, the TNM has several limitations:

1) It primarily relies on anatomic/pathological characteristics of the tumor and includes very limited molecular information;

2) It does not fully capture tumor biology/heterogeneity, leading to inconsistencies in prognosis and treatment recommendations;

3) The system is complex and requires an accurate assessment of tumor characteristics;

4) It lacks clarity regarding the assessment of lymph node involvement (ie,isolated tumor cells, micro-metastases, extranodal extension, and so on);

5) It only provides a snapshot of the status of the tumor at the time of diagnosis but does not take into account response to treatment or tumor progression; and

6) It does not incorporate circulating tumor markers (eg, CEA), which can provide valuable information regarding treatment response and disease progression over time

EDITORIAL

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Commentaries & Educational Content

See "Pathological-features-modified TNM staging system improves prognostic accuracy for rectal cancer" by Yuesheng Yang et al on p. 645

The TNM staging system of the American Joint Committee on Cancer (AJCC) staging classification, combined with other clinical and molecular findings, is the basis for making informed treatment decisions and prognostic assessment for patients with colon and rectal cancer. The current eighth edition was published in 2016 and implemented in 2018. Despite its worldwide use, the TNM has several limitations: 1) it primarily relies on anatomic/pathological characteristics of the tumor and includes very limited molecular information; 2) it does not fully capture tumor biology/heterogeneity, leading to inconsistencies in prognosis and treatment recommendations; 3) the system is complex and requires an accurate assessment of tumor characteristics; 4) it lacks clarity regarding the assessment of lymph node involvement (ie, isolated tumor cells, micrometastases, extranodal extension, and so on); 5) it only provides a snapshot of the status of the tumor at the time of diagnosis but does not take into account response to treatment or tumor progression; and 6) it does not incorporate circulating tumor markers (eg, CEA), which can provide valuable information regarding treatment response and disease progression over time.

In addition, over the past 10 to 20 years, the TNM staging system has been updated several times. During this period, the main controversy has concentrated around tumor deposits (TDs) or tumor nodules. These are small clusters or aggregates of cancer cells, found in the pericolonic or perirectal fat, adjacent to the primary tumor site, in up to 20% of patients with colorectal cancer who undergo radical surgery. The seventh and eighth editions of the TNM staging system contain important differences in the definition of TDs, and in the current eighth edition, the shape, contour, and size of the deposit are no longer considered in their definition. Despite the strong evidence that TD-positive patients have poor overall survival, and that TDs are also an independent prognostic factor for survival in patients with distant metastasis,[1] the latest version of TNM staging only considers TDs without lymph node metastasis (pN1c). The latest version of the TNM also neglects the importance of the number of TDs, as it has been reported that the greater the number of TDs, the worse the prognosis.[2] As there is a lack of clarity regarding TDs, some authors have proposed that, in view of their prognostic implication, they should be included in an M category rather than in the T or N categories, whereas others favor a novel N category in which TDs are counted as metastatic lymph nodes.

In this issue of *Diseases of the Colon & Rectum*, Yang et al[3] reported on a novel pathological features–modified TNM (TNM-P) staging system in predicting survival for patients with rectal cancer. The TNM-P has been developed using a previously reported machine learning algorithm, ensemble algorithm of clustering of cancer data, which uses information from various models using multiple clustering algorithms to improve predictive performance in comparison to a single model. The proposed staging was retrospectively tested in 14,468 patients diagnosed with rectal adenocarcinoma from the Surveillance, Epidemiology, and End Results database between 2010 and 2015. A development cohort included 9023 patients who underwent surgery as the primary treatment while the validation group consisted of 5445 patients who received neoadjuvant therapy followed by surgery. The multivariable Cox regression analysis identified 3 pathological

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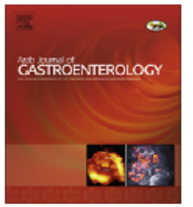

Editorial

Can a major change in classification, staging and grading of rectal cancer improve planning for treatment, reporting and outcome of the disease?

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Original research

TNMF versus TNM in staging of colorectal cancer

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HIGHLIGHTS

- TNM staging of colorectal cancer has undergone minimal changes during the past 20 years despite their impact on the prognosis.
- In this Paper we drew the attention to several risk factors of colorectal cancer that are not included in the TNM system.
- We suggest the addition of 'F' to the TNM system to include the continuous expanding list of risk factors of colorectal cancer.

Aim:

- TNM staging and histological grading of rectal cancer has undergone no or minimal changes during the past 20 years despite their major impact on planning, reporting and outcome of the disease.

- The addition of category “F” to the “TNM” staging of colorectal cancer, which becomes TNMF will accommodate the expanding list of risk factors that may affect the management and thus avoid squeezing them into the TNM categories.

Methods:

- Reporting of the following risk factors was traced in 730 (664 retrospective and 66 prospective) cases of colorectal cancer: age, Tumor location, preoperative CEA, intraoperative tumor perforation and blood transfusion, quality of TME, tumor grade, non nodal T.Ds, Lymph-vascular invasion, lymph node ratio, circumferential tumor margins, apical lymph nodes, infiltrating or pushing and K-ras gene mutation.

PATIENTS AND METHODS

Patients and methods

- ***<u>Population of study and disease condition</u>***

Patients of both sexes and all age groups with colorectal cancer were included in the study.

Patients and methods

Exclusion criteria

- 1- Primary anal cancer.
- 2- Patient with known malignancy with no 1ry resection.
- 3- Tumours other than AdenoCarcinoma Pathology and its Variants.

Inclusion criteria

- 1- Cases of resectable colorectal malignancies.
- 2- Adenocarcinoma pathology with all its variant, for example mucinous and signet ring (not melanoma or squamous cell carcinoma).

Intervention

- Several risk factors were monitored in patients with colorectal cancer and reported in the preoperative period , during the operation and in the post operative period:
- Pre-operative CEA.
- Location of tumor and age of the patient.
- IOBT (Intraoperative Blood Transfusion).

Interventions

- IOTP
- TNM stage
- Grade of the tumor
- LNR
- Non nodal T.Ds
- Lymphovascular invasion
- Circumferential tumor margins
- Infiltrative vs. pushing
- Apical L.Ns
- K-ras gene mutation

Interventions

These was done in two groups of patients:

- Retrospective cases from the files and database of colorectal cancer patients among different centers in Egypt including Cairo university hospitals, Ain Shams university hospitals and Alexandria university hospitals.
- Prospective group of colorectal cancer patients presenting to Cairo university hospitals in the period between 7/2012 and 1/2014.
- Prospective group was considered an intervention group to detect the difference in reporting and response between retrospective and prospective groups.

Interventions

Response of the treating oncologist:

The response of the treating oncologist was traced by following the post-operative adjuvant treatment received by the patients in the following sub group analysis:

- 1- T2N0M0 in colonic and rectal carcinoma in both retrospective and prospective groups of patients.
- 2- T1-2N1-2M0 in colonic and rectal adenocarcinoma in both retrospective and prospective groups of patients.
- 3- T3N0M0 in colonic and rectal adenocarcinoma in both retrospective and prospective groups of patients.

Statistics

- Data were statistically described in terms of frequencies (number of cases) and percentages when appropriate. Comparison between the study groups was done using Chi square (χ^2) test. Exact test was used instead when the expected frequency is less than 5. *P* values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS.

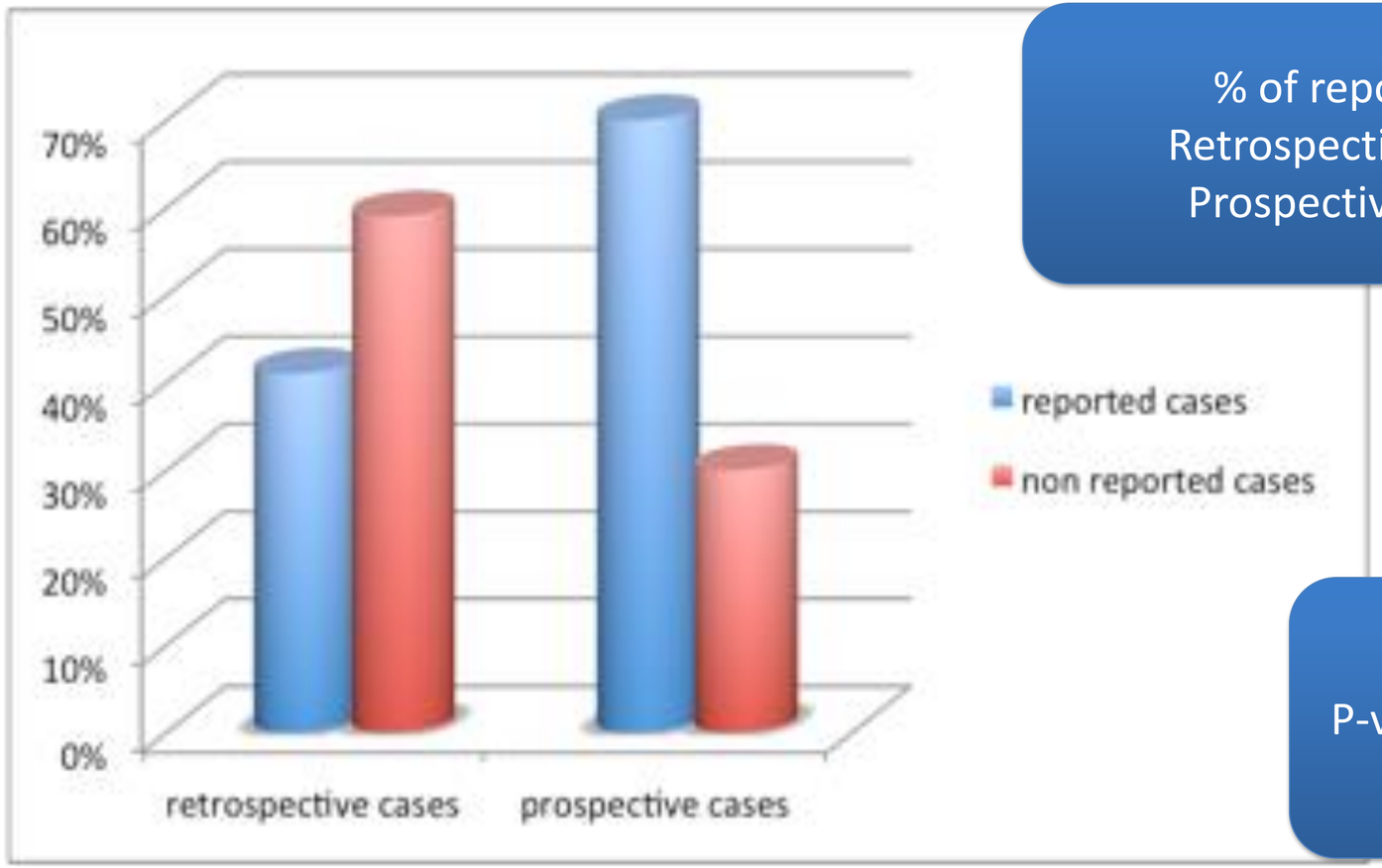
Results

Reporting

Results

1-Age and location

2-Pre-operative CEA

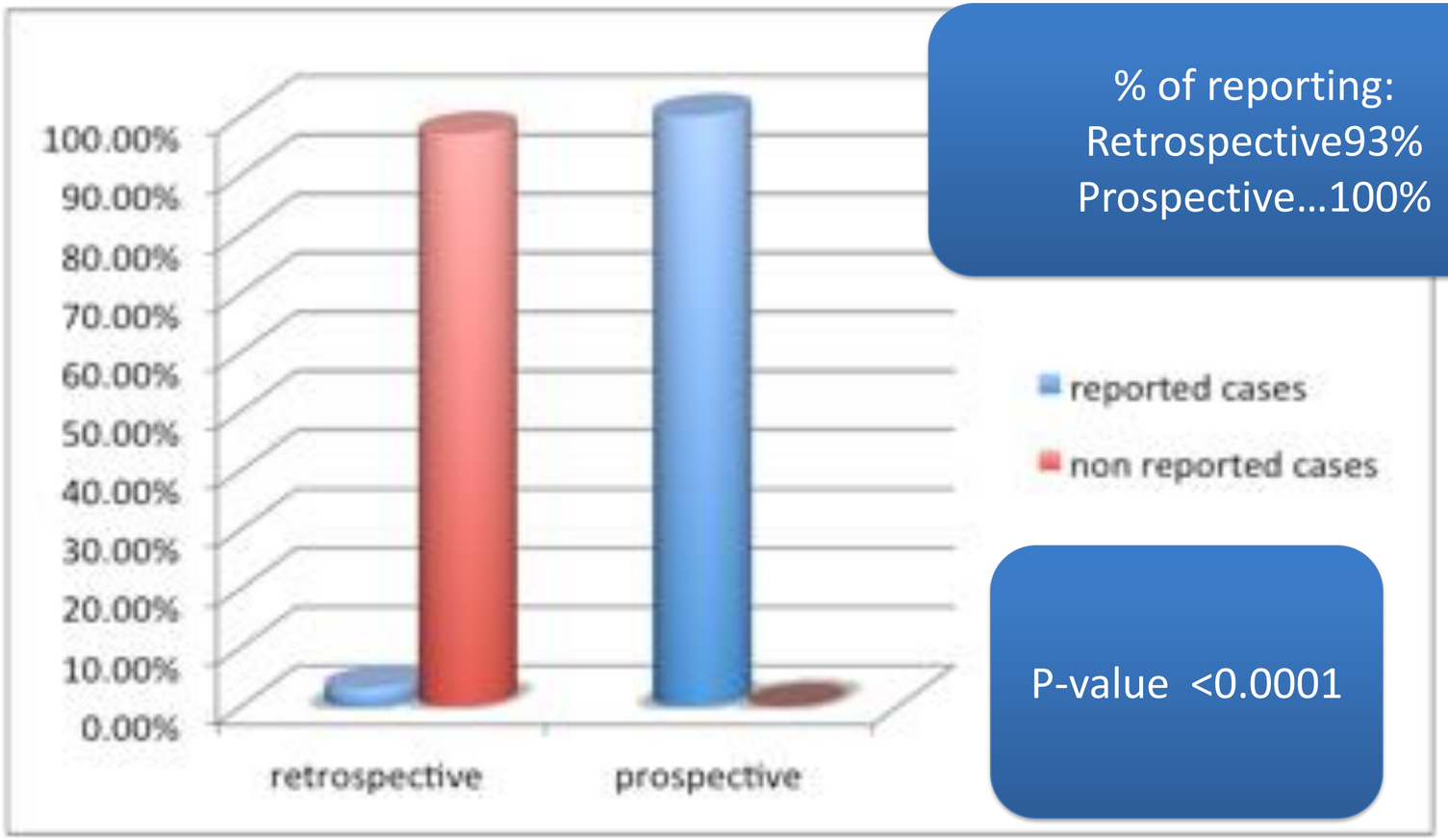


% of reporting:
Retrospective…41%
Prospective…70%

P-value <0.0001

Results

3-IOBT

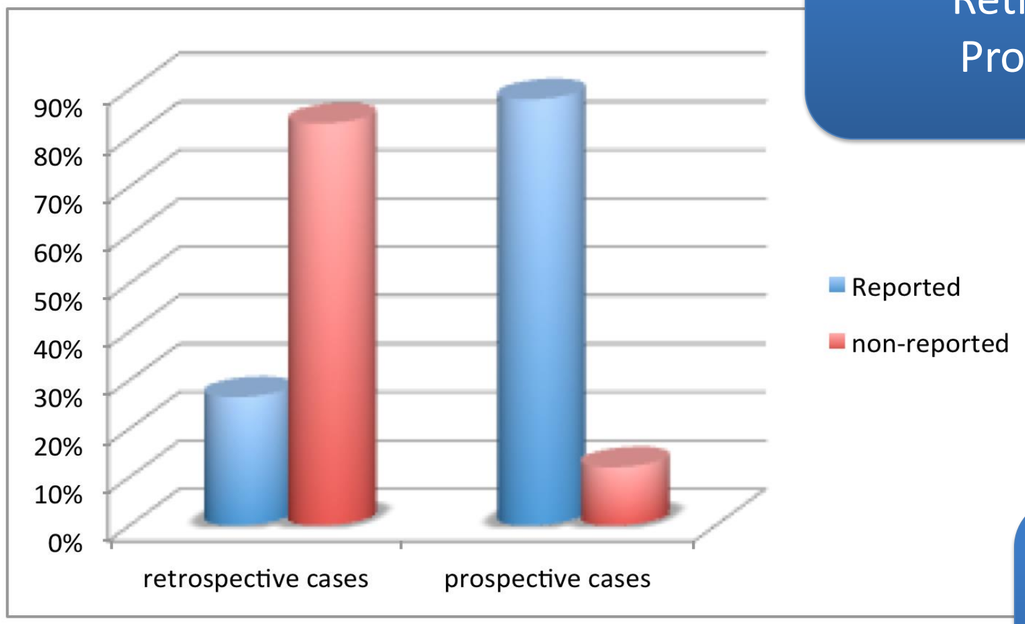


% of reporting:
Retrospective93%
Prospective…100%

P-value <0.0001

Results

- 4-IOTP

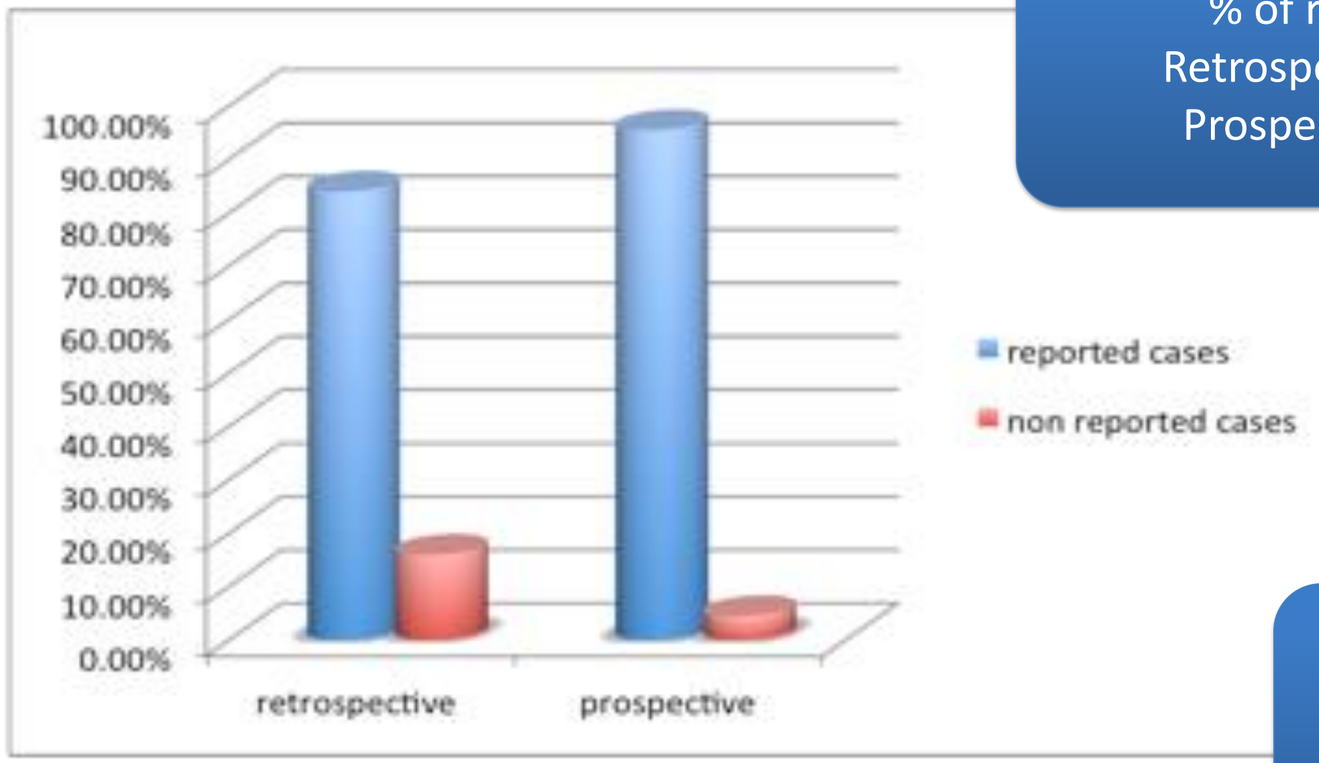


% of reporting:
Retrospective…27%
Prospective…100%

P-value <0.0001

Results

- 5-TNM stage

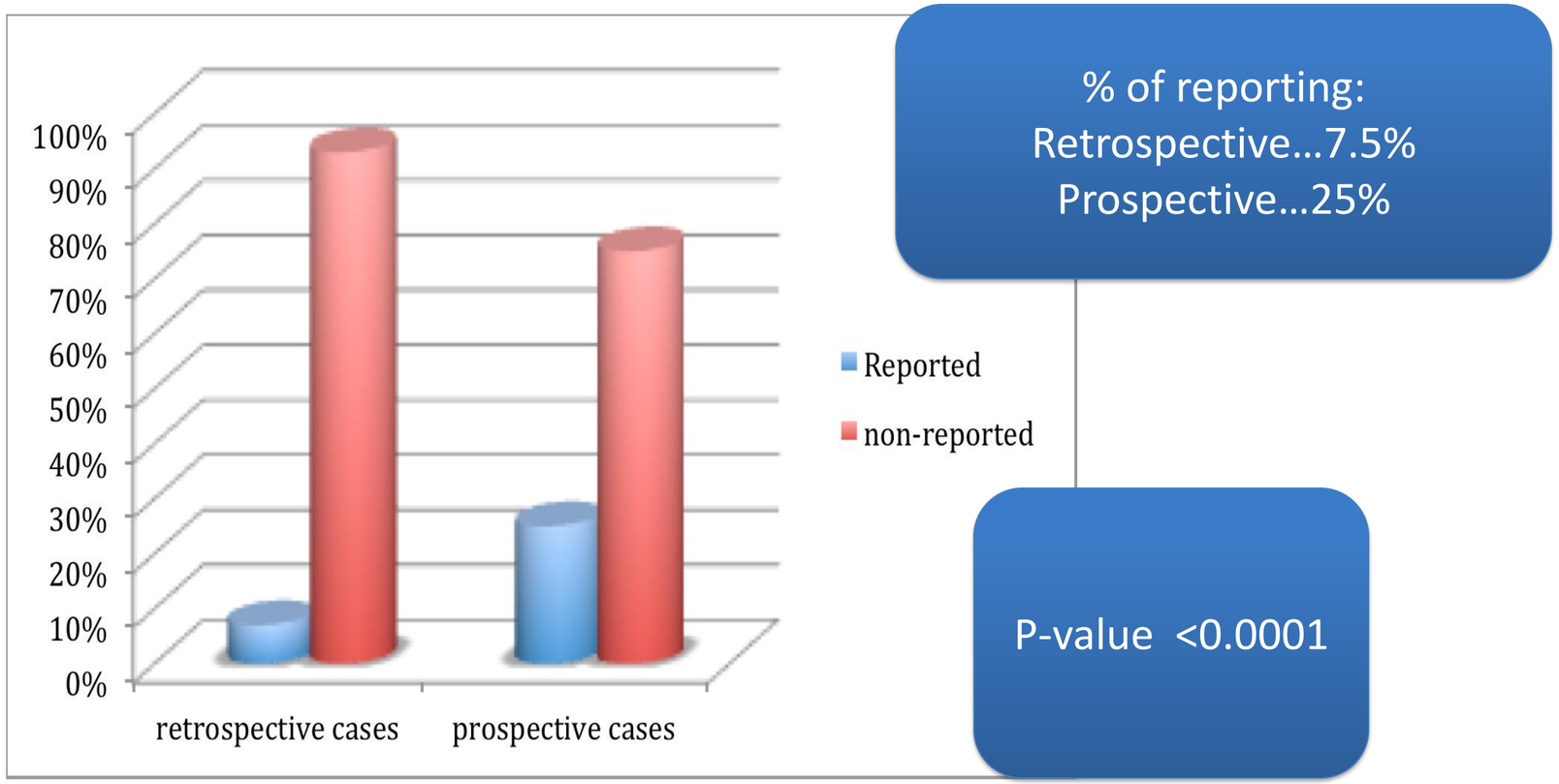


% of reporting:
Retrospective…83%
Prospective…95%

P-value =0.021

Results

- 6-Non-nodal T.Ds

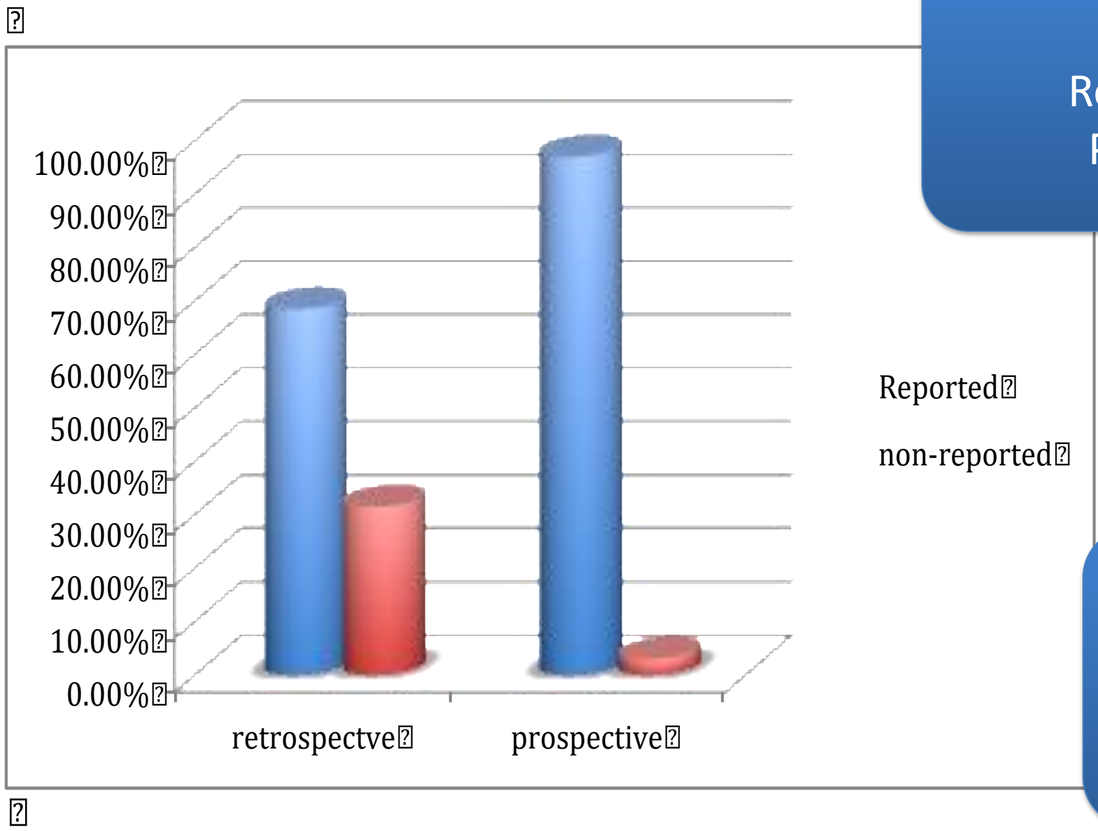


% of reporting:
Retrospective…7.5%
Prospective…25%

P-value <0.0001

Results

- 7-Grade of tumor:

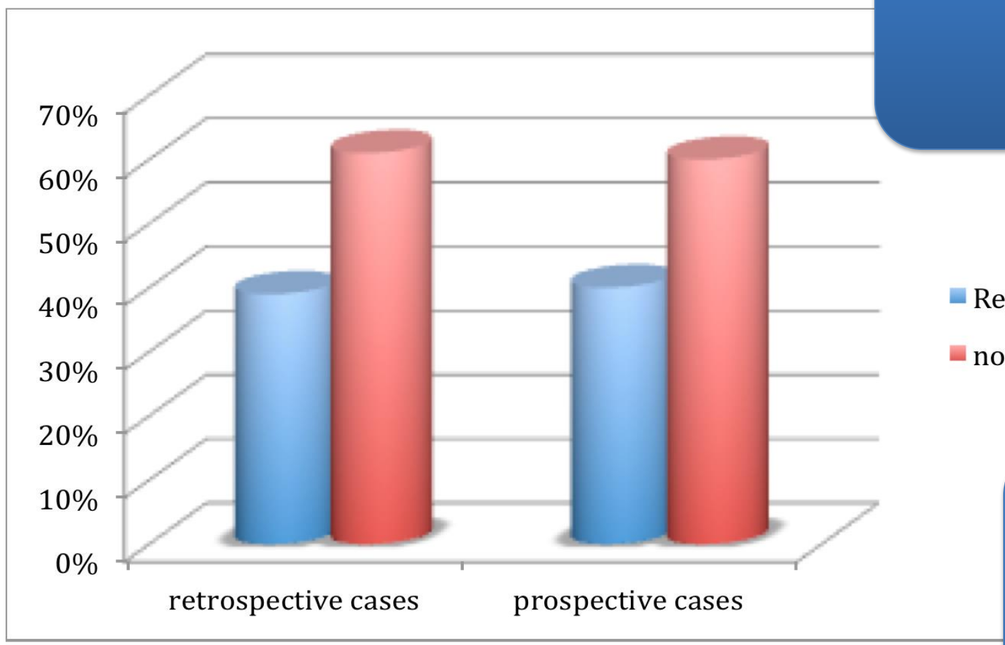


% of reporting:
Retrospective…68%
Prospective…97%

P-value <0.0001

Results

- 8-LVI:

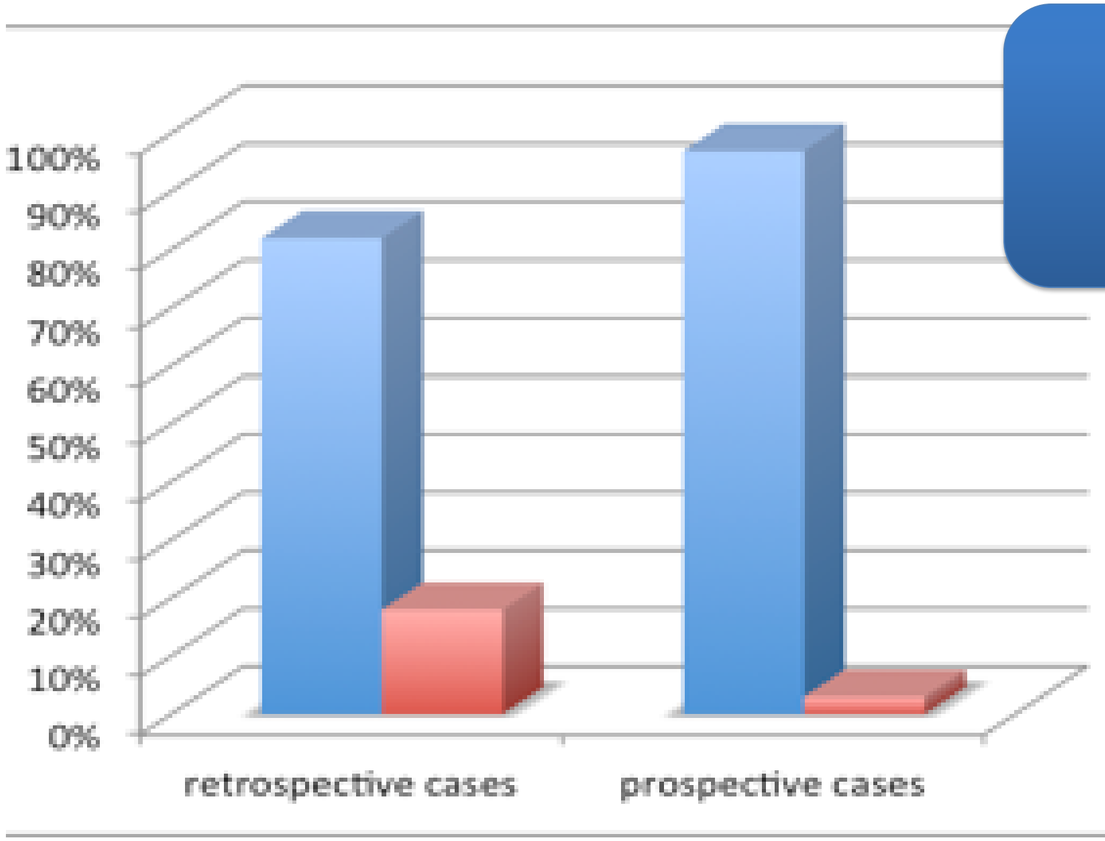


% of reporting:
Retrospective…39%
Prospective…41%

P-value =0.8561

Results

9-LNR

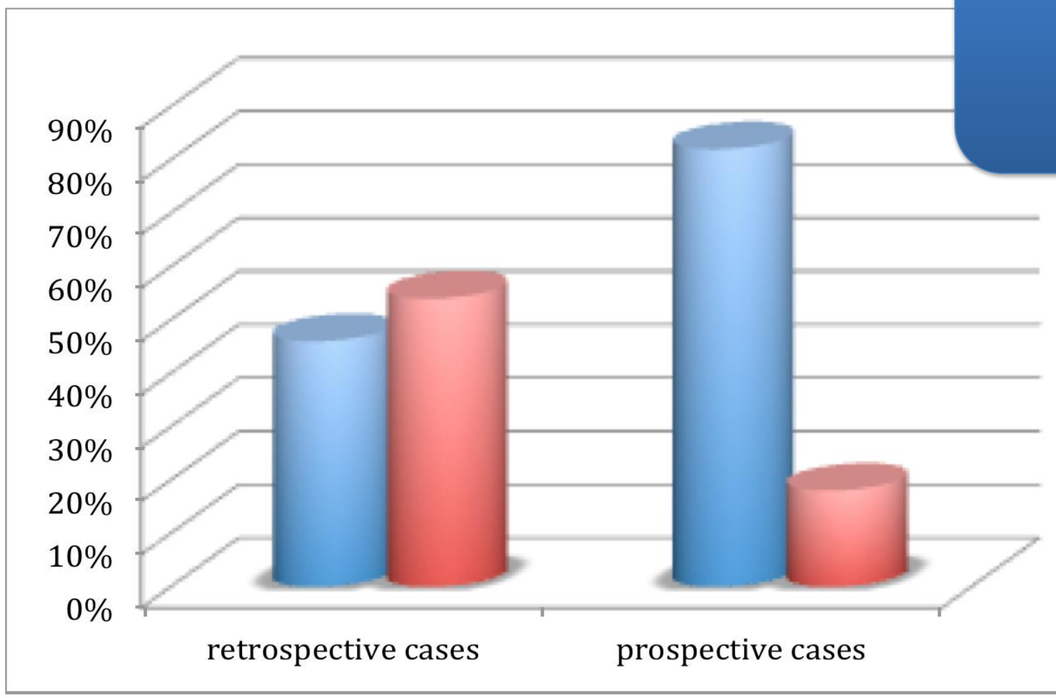


% of reporting:
Retrospective…83%
Prospective…97%

P-value =0.004

Results

- 10.CRM

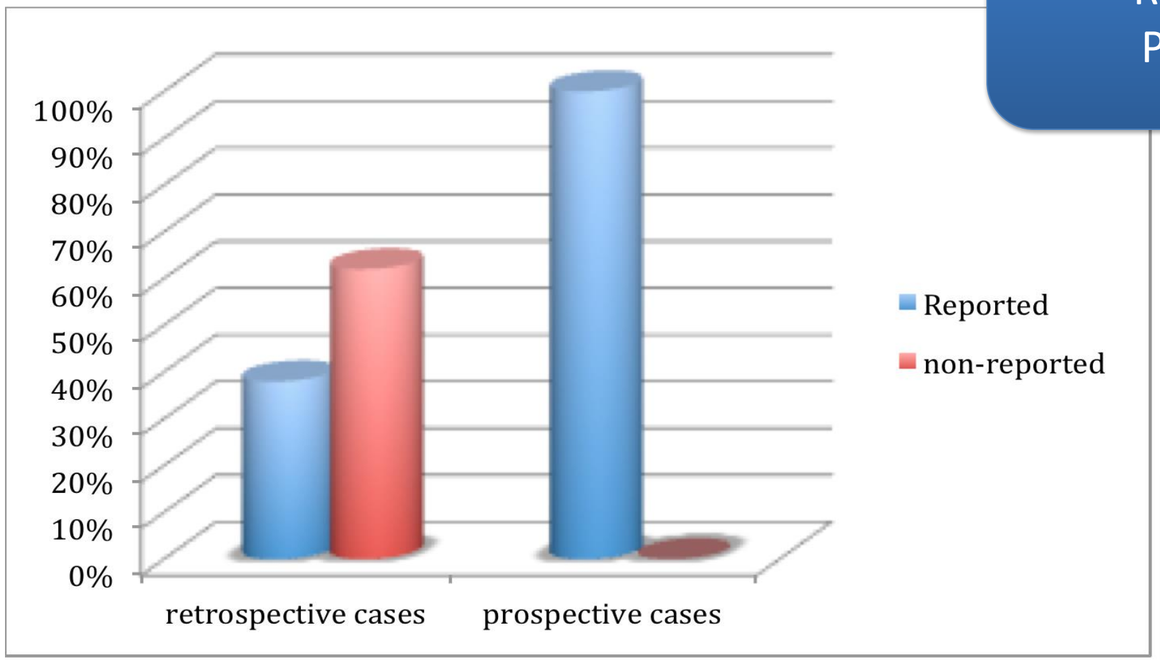


% of reporting:
Retrospective…46%
Prospective…82%

P-value <0.0001

Results

- 11.Quality of TME

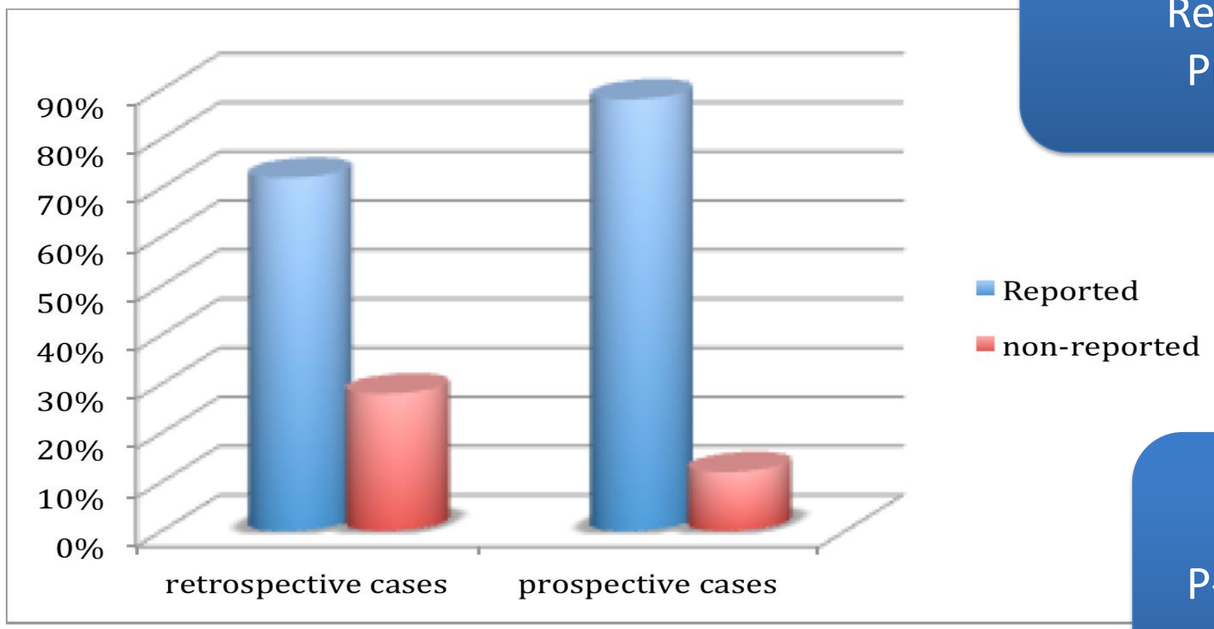


% of reporting:
Retrospective…38%
Prospective…100%

P-value <0.0001

Results

- 12.Infilterative vs. Pushing margins

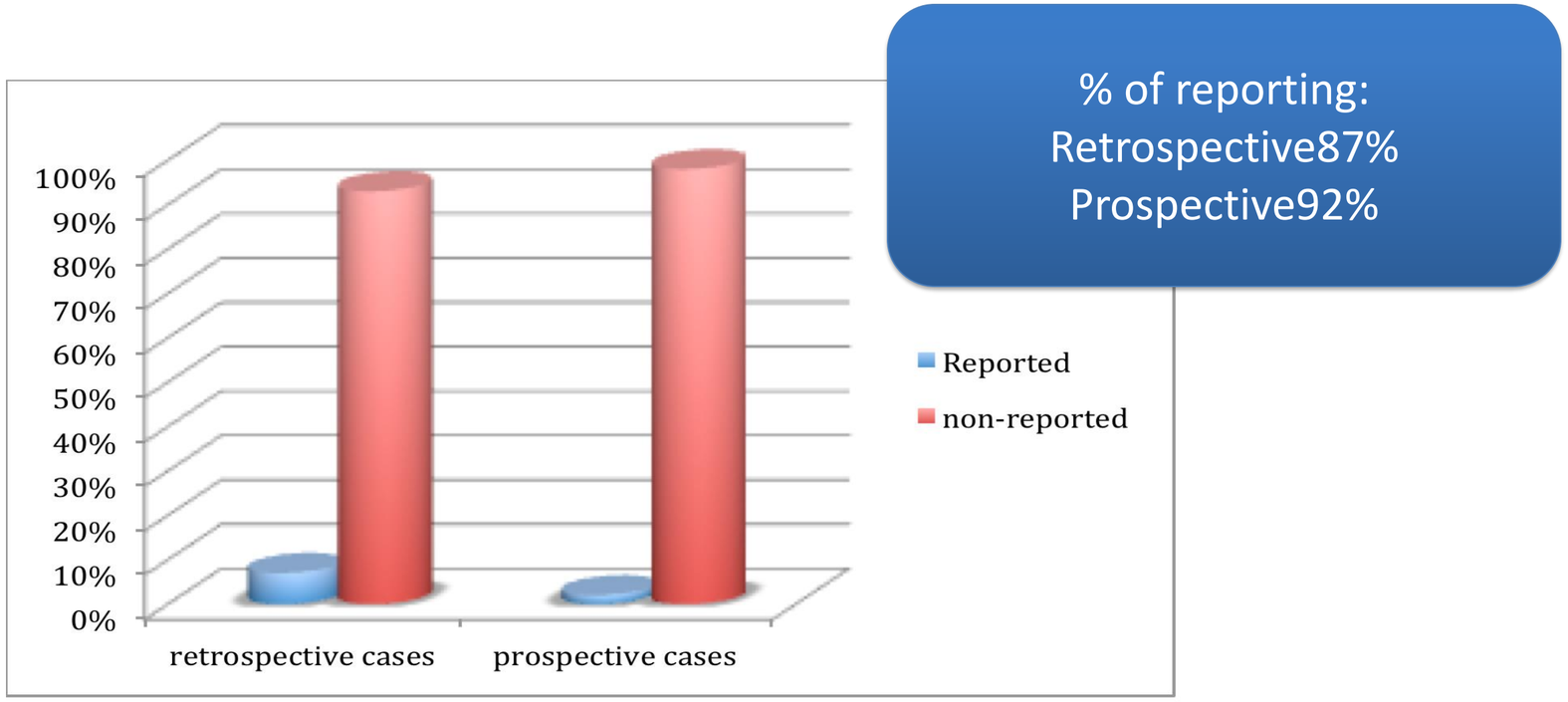


% of reporting:
Retrospective…72%
Prospective…88%

P-value =0.008

Results

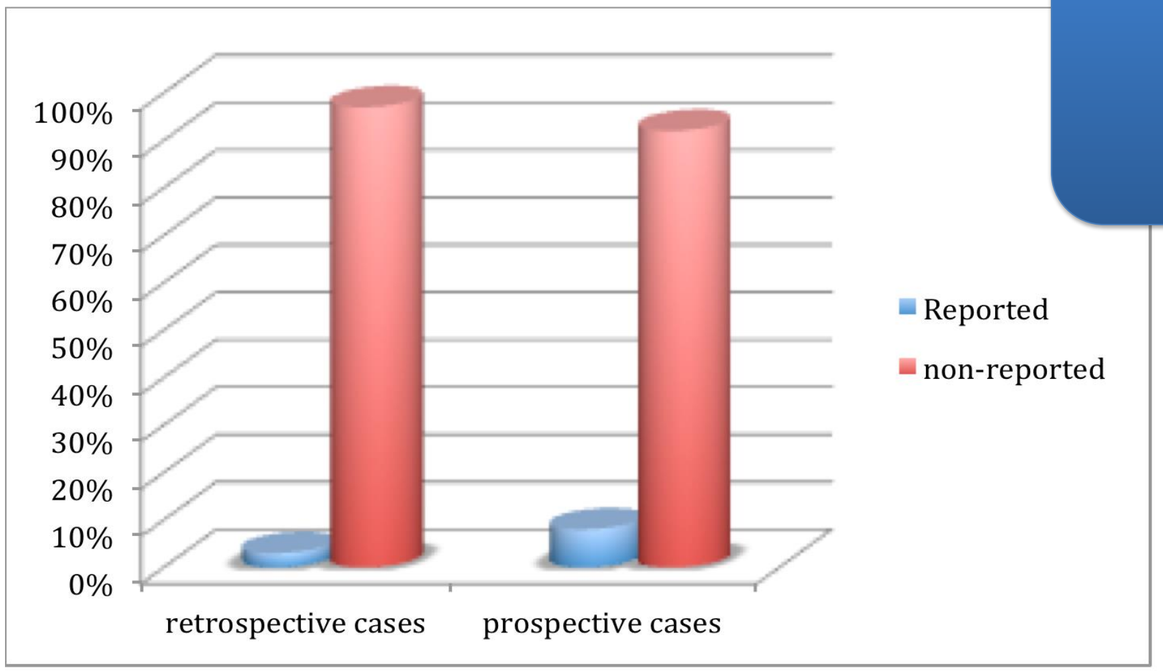
- 13. K-ras gene mutation



% of reporting:
Retrospective87%
Prospective92%

Results

- 14. Apical L.Ns



% of reporting:
Retrospective 94%
Prospective 88%

P-value =0.186

Results

Response

- T1-2 N0 M0:

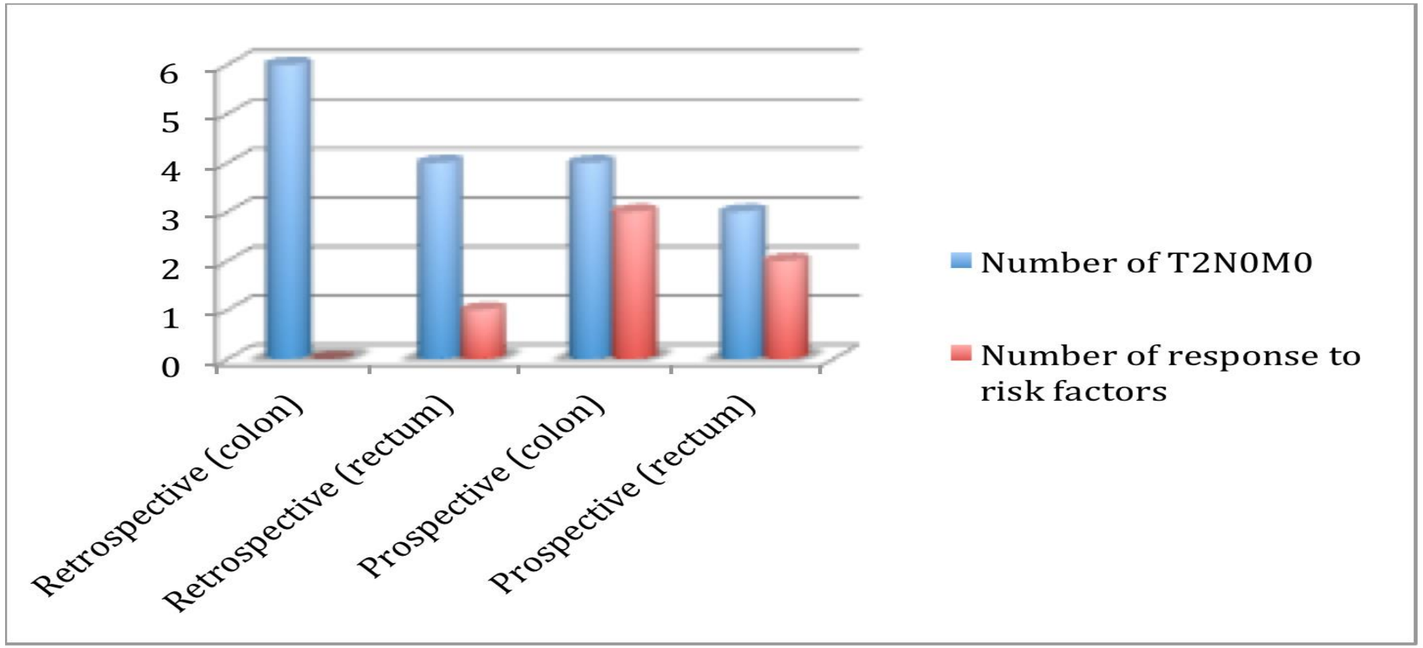
Percentage of response was as follows:

1.Retrospective colon cases…0%
2.Prospective colon cases…75%
P-value=0.011

3.Retrospective rectum cases…25%
4.Prospective rectum cases…67%
P-value=0.27

Results

- Graph representing response to T1-2 N0M0



Results

- T1-2 N1-2 M0

Response was as follows:

1.Retrospective colon cases…0 from 2 cases

2.There were no prospective colon cases

3.Retrospective rectum cases…0 from 2

4.Prospective rectum cases…1 from 1

Results

- T3 N0 M0

Percentage of response was as follows:

1.Retrospective colon cases…38%

2.Prospective colon cases…55%

P-value=0.341

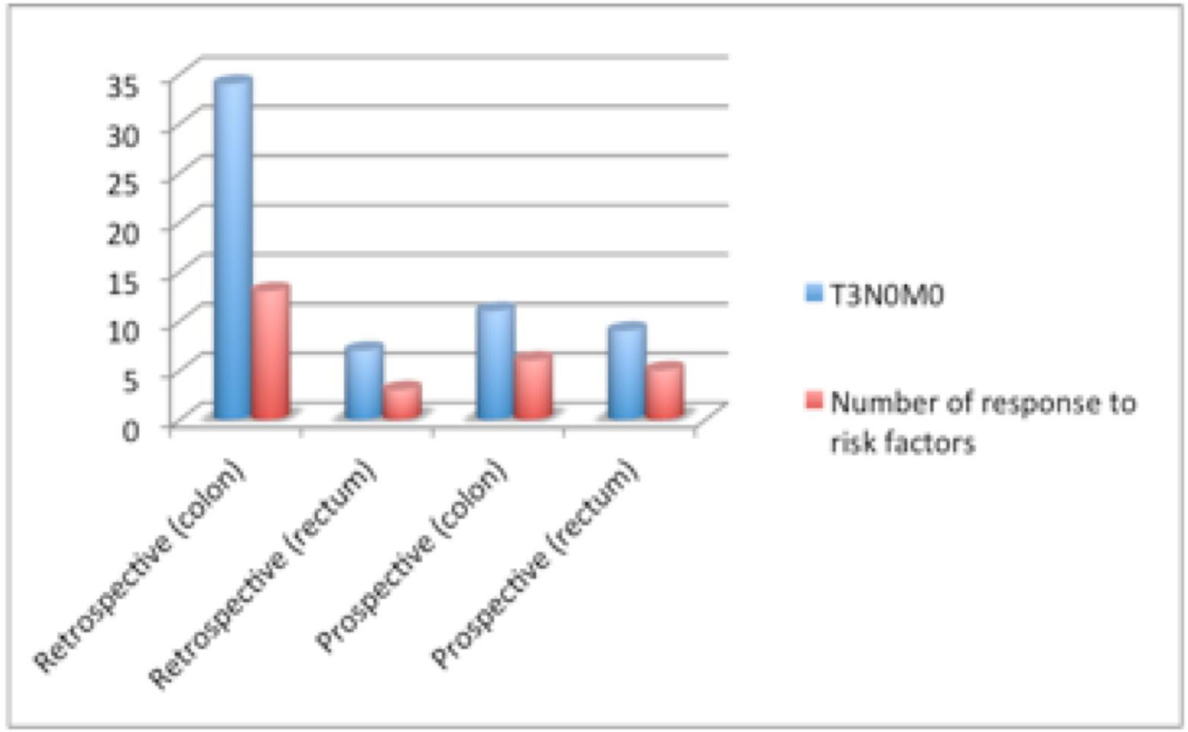
3.Retrospective rectum cases…43%

4.Prospective rectum cases…56%

P-value=0.641

Results

- Graph representing response to T3N0M0



Discussion

Discussion

- The difference between reporting of pre-operative CEA, intra-operative tumor perforation, intra-operative blood transfusion, non-nodal T.Ds, grade of the tumor, Quality of total Mesorectal excision and Circumferential tumor margins between both groups (retrospective and prospective cases) shows very high statistical significance with **P-value for all <0.0001**

Discussion

- However difference between reporting of other risk factors shows a statistical significance. This includes reporting of TNM stage **(P-value=0.021),** Lymph node ratio **(P-value=0.04)** and infiltrative vs pushing margins **(P-value=0.008).**
- On the other hand difference of reporting of other factors shows no statistical significance. This includes apical L.Ns affection **(P-value=0.185)** and Lymphovascular invasion **(P-value=0.8651).**

Discussion

- <u>There is statistically significant improvement in the response of the oncologist between both groups in T1-2 N0 M0 colon cases **(P-value=0.011).**</u>
- Although there is minimal improvement in response in T1-2 N1-2 M0 rectal cases but it is statistically not significant **(P-value=0.27).**
- There was no statistically different significance in response between both groups in T1-2 N1-2 M0 rectum cases **P-value=0.083,** although there is numerical improvement regarding percentage of response.

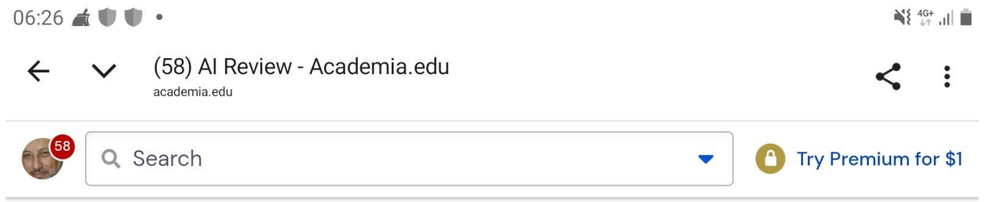
Discussion

- There was an improvement in response but with no statistical significance in T3N0M0 colon cases ***P-value=0.341***
- Also there was an improvement in response but with no statistical significance in T3N0M0 rectum cases ***P-value=0.614***

Conclusion

- Addition of category “F” to TNM staging system to be TNMF may warn the clinician of the need for more aggressive treatment strategies in those patients with early TNM staging with one or more risk factors. Much more importantly, it is also to avoid ignoring the already established risk factors due to our inability to accommodate them in the already inhospitable TNM categories

A.I Review on Academia.com



AI Review of "TNMF versus TNM in Staging of Colorectal Cancer"

Overview

The paper investigates the potential enhancement of the TNM staging system for colorectal cancer by introducing an additional 'F' category to acknowledge a broader array of risk factors not encompassed by the existing system. Documenting the inadequacy in recognizing prognostic factors such as K-ras mutation and lymphovascular invasion, the study traces these risk factors in both retrospective and prospective cohorts. Ultimately, it aims to demonstrate that the addition of an 'F' category could increase reporting accuracy and influence treatment plans. Such a revision is proposed to assist clinicians in acknowledging important risk considerations.

A.I Review on Academia.com

CONAKRY J. 2023, doi:10.11648/j.crj.20231101.11.

Strengths

This work is commendable for its insightful proposal to refine current cancer staging methods, emphasizing the insufficiency of the TNM system by demonstrating improvements in risk factor reporting with the introduction of the 'F' category. The paper's methodological approach—retrospectively and prospectively evaluating a comprehensive array of risk factors—provides a robust set of data supporting its thesis. The clear articulation of key prognostic factors could have significant implications for clinical practice, enabling more individualized and effective treatment plans and highlighting an area that remains underexplored in clinical oncology.

A.I Review on Academia.com

Reviewer Commentary

This paper raises important questions about the intersections of traditional and novel factors affecting cancer prognostics and management, stimulating discourse on how to bridge gaps between complex medical data and practical healthcare applications. The incorporation of a more complete spectrum of risk factors into staging systems could potentially revolutionize how diagnoses inform treatment strategies.

Summary Assessment

Overall, this work represents a valuable contribution to colorectal cancer research by challenging the adequacy of traditional staging protocols. The proposed addition of the 'F' category signifies a step toward a more nuanced understanding of cancer prognosis, potentially guiding future revisions of staging frameworks. The study successfully forwards a meaningful conversation on enhancing clinical precision in oncological practice, opening avenues to further interdisciplinary exploration and refinement of cancer treatment strategies.

ORIGINAL CONTRIBUTION

Pathological-Features-Modified TNM Staging System Improves Prognostic Accuracy for Rectal Cancer

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Yuesheng Yang and Zifeng Yang contributed equally to this work.

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CONCLUSIONS: The proposed pathological-features-modified TNM staging could complement the current TNM staging by improving the accuracy of survival estimation of patients with rectal cancer. See **Video Abstract**.

EL SISTEMA DE ESTADIFICACIÓN TNM CON CARACTERÍSTICAS PATOLÓGICAS MODIFICADO MEJORA LA PRECISIÓN DEL PRONÓSTICO DEL CÁNCER DE RECTO

ANTECEDENTES: Se observan variaciones en los resultados de supervivencia en el sistema de estadificación TNM del Comité Conjunto Americano del Cáncer 8º edición

EDITORIAL

Outcome Prediction in Rectal Cancer Beyond the Current TNM System—An Unmet Need

Manuel Rodriguez-Justo, M.D., F.R.C.Path.[1,2]

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2 Department of Oncopathology, Cancer Institute, University College London, United Kingdom

See "Pathological-features-modified TNM staging system improves prognostic accuracy for rectal cancer" by Yuesheng Yang et al on p. 645

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In addition, over the past 10 to 20 years, the TNM staging system has been updated several times. During this period, the main controversy has concentrated around tumor deposits (TDs) or tumor nodules. These are small clusters or aggregates of cancer cells, found in the pericolonic or perirectal fat, adjacent to the primary tumor site, in up to 20% of patients with colorectal cancer who undergo radical surgery. The seventh and eighth editions of the TNM staging system contain important differences in the definition of TDs, and in the current eighth edition, the shape, contour, and size of the deposit are no longer considered in their definition. Despite the strong evidence that TD-positive patients have poor overall survival, and that TDs are also an independent prognostic factor for survival in patients with distant metastasis,[1] the latest version of TNM staging only considers TDs without lymph node metastasis (pN1c). The latest version of the TNM also neglects the importance of the number of TDs, as it has been reported that the greater the number of TDs, the worse the prognosis.[2] As there is a lack of clarity regarding TDs, some authors have proposed that, in view of their prognostic implication, they should be included in an M category rather than in the T or N categories, whereas others favor a novel N category in which TDs are counted as metastatic lymph nodes.

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These criticisms should not obscure the valuable information that is reported in this study, but there is room for improvement in the risk stratification and prognosis by incorporating additional pathological features and nonanatomic prognostic factors such as:

1. Mismatch repair protein deficiency: The prevalence of

adjuvant treatment in rectal cancer.

2. K-*ras*/*BRAF* mutation status: It has been shown that there is a statistically significant increase in the performance of models when K-*ras*/*BRAF* mutation and MSI
3. Tumor budding (TB): TB, defined as microscopic clusters of undifferentiated cancer cells just ahead of the invasive front of the tumor, has been variably ignored,

4. Host lymphoid response to tumor: Nongenetic markers, mainly related to the microenvironment (ie, tumor-infiltrating lymphocytes, gene expression signatures as surrogate markers of the epithelial–mesenchymal transition, activated cancer-associated fibroblasts, and so on), have demonstrated independent prognostic value in colorectal cancer.[12] Some of these markers appear to define an immunosuppressive microenvironment and resistance to standard chemotherapy.

current eighth edition of AJCC TNM classification for colorectal cancer can be improved by additional modifications, integrating genomic sequencing, circulating tumor DNA analysis, and imaging multiomics to better understand tumor heterogeneity.

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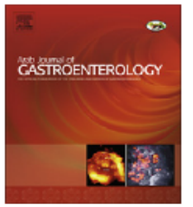

Editorial

Can a major change in classification, staging and grading of rectal cancer improve planning for treatment, reporting and outcome of the disease?

International Journal of Surgery 27 (2016) 147–150

Contents lists available at ScienceDirect

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Original research

TNMF versus TNM in staging of colorectal cancer

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HIGHLIGHTS

- TNM staging of colorectal cancer has undergone minimal changes during the past 20 years despite their impact on the prognosis.
- In this Paper we drew the attention to several risk factors of colorectal cancer that are not included in the TNM system.
- We suggest the addition of 'F' to the TNM system to include the continuous expanding list of risk factors of colorectal cancer.

THANK YOU

Begin forwarded message:

From: Taris Truax <em@editorialmanager.com>
Date: August 18, 2024 at 3:50:36 PM GMT+3
To: Mohamed Yehia Elbaemelgi <dr.yeho@yahoo.com>
Subject: Notice of Decision - DCR Letter to the Editor: TNMF Vs. TNM in staging of colorectal cancer DCR-D-24-00345R1 - [EMID:5ff230517c3e767d]
Reply-To: Taris Truax <tarisashton@gmail.com>

08/18/2024

RE: "Letter to the Editor: TNMF Vs. TNM in staging of colorectal cancer" by Dr Mohamed Yehia Elbaemelgi
DCR-D-24-00345R1

Dear Dr Mohamed Yehia Elbaemelgi,

We are pleased to inform you the above referenced Letter to the Editor has been accepted by the Editor for publication in Diseases of the Colon & Rectum. Please note, we have requested a reply from the authors of the article you reference. If the authors wish to provide a reply, your letter will be held for production until their response is received and accepted by the Editor.

You will receive a FINAL acceptance letter when the above referenced letter moves to production.

Please feel free to contact us with any questions.

Best regards,

Taris Truax
Editorial Assistant
Diseases of the Colon & Rectum
https://www.editorialmanager.com/dcr/