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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.

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ABSTRACT

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, Lymphovascular invasion, lymph node ratio, circumferential tumor margins, apical lymph nodes, infiltrating or pushing and K-ras gene mutation.

Results: The reporting of most risk factors was inadequate; also there is marked improvement in reporting in the prospective cases in preoperative CEA, intra operative blood transfusion and tumor perforation, quality of TME, tumor grade and non-nodal T.Ds (P-value <0.0001).

Conclusion: The addition of category 'F' to the TNM staging system to become TNMF may avoid ignoring already established risk **factors** due to our inability to accommodate them in the inhospitable TNM categories.

1. Background

The value of all grading and staging systems of cancers is to inform on the prognosis and the plan of treatment. The Dukes [1] staging was the first in coloproctology to address the issue of prognosis. It is still very widely used through out the world. In UK it is encouraged to combine the Dukes staging with the other widely used T (tumor) N (node) M (metastasis) system. There are prefixes preceding the TNM to indicate certain event like the prefix 'p' indicating the pathological anatomical report, the prefix 'y' for the preoperative treatment and the prefix 'u' which refer to ultrasonic diagnosis. TNM is applicable to all forms malignancies and has been seen frequent bouts of evolutions and transformations [2].

Classification (TNM) staging and histologic grading of rectal cancer has undergone no or minimal changes during the past 20 years despite their major impact on planning, reporting and

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outcome of the disease. The addition of a letter (R) (for prognostic risk factors either microscopic or macroscopic) to the TNM as TNM'R' 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. This category obviates the need to squeeze those factors into the traditional TNM, for example, version 6, or, more recently, version 7. These changes would hypothetically improve the overall outcome of the disease. The value of all grading and staging systems of cancers is to inform on the outcome, be it with or without treatment [3].

For example of this risk factors is the extranodal tumor deposits (TD), which was defined by the 6th edition of TNM as follows:

" A tumor nodule in the pericolic/perirectal adipose tissue without histological evidence or residual lymph node in the nodule is classified in the 'pN' category as a regional lymph node metastasis, as the nodule has the form and smooth contour of a lymph node. If the nodule has an irregular contour, it should be classified in the 'T' category and also coded as 'V1' (microscopic venous invasion) or 'V2', if it was grossly evident, because there is a strong likelihood that it represent venous invasion [4].

Similarly, Nagtegaal and Quirke have recently reviewed the literature with regard to extra-nodal tumor deposits (TDs) and concluded that the 3-mm rule in the fifth edition or contour in the sixth edition have no supporting evidence. Therefore, TDs should not be classified as positive lymph nodes after neo-adjuvant therapy as the presence of tumor micro foci may represent good tumor response and successful treatment and not an adverse sign [5].

The TNM classification, in its current status, does not address the other risk factors which were proved to affect the prognosis by reported high-quality evidence-based research in the field such as; intravascular and intralymphatic invasion where this invasion indicates that the tumor may metastasize to the regional L.Ns more often. These tumors also recurred at systemic lymph nodes after curative intent surgery more often [6].

Other risk factors include type of advancing margin of the tumor (infiltrative vs. Pushing) where a good prognosis for Dukes A, B and C1 patients were usually associated with pushing tumors in the contrast to C1 and C2 patients with infiltrating tumors which had had a poor prognosis. Also occult tumor cells in lymph nodes (NO+) developed a local relapse and/or distant metastases while patients without occult tumor cells (NO-) but with no effect on overall survival [7].

Several additional histopathological variables not directly related to staging but having independent prognostic significance have been included in current pathology reporting protocols, for example histological tumor type [8] and lymphatic and vascular invasion [9].

There are several prognostic risk factors which have very strong impact on the prognosis during post operative management, these risk factors may include histological tumor type [8,9], tumor grade and differentiation [8,9], circumferential margins status [10,11], Lymphovascular invasion[10,11].

2. Aim of work

Modification of the TNM staging of colorectal cancer into TNMF which is suggested to be as follows:

TNM: as TNM described in the literature.
F: Other risk **factors** that may affect the management which will be discussed in this study. The value of adding a separate category 'F' to the already established TNM to be TNM'F', for the continuously expanding list of risk factors, is to avoid squeezing them into the already established TNM categories, warning 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 such as location of the rectal cancer, lymphovascular invasion or tumor markers and ploidy due to our inability to accommodate them in the already inhospitable TNM categories.

3. Patients and methods

3.1. Study objectives

The first end point is to identify the frequency of reporting of the risk factors associated with operable colorectal malignancy not included in the traditional TNM, which are important for treatment guidance.

The second end point is the possibility of improving the frequency of reporting of the well established risk factors other than TNM.

3.2. The study hypothesis

There are many risk factors that have been proved to be associated with bad prognosis of colorectal cancer which are important to consider when planning treatment to improve prognosis and possibility of the suggested TNMF to improve the frequency of reporting and improving the physician response to those risk factors not normally included in the traditional TNM.

4. Study methods

4.1. Population of study and disease condition

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

4.2. Inclusion criteria

1 Cases of resectable colorectal malignancies.
2 Adenocarcinoma pathology with all its variant, for example mucinous and signet ring.

4.3. Exclusion criteria

1 Patients with primary anal cancer.
2 Patients with known malignancy without 1ry resection.
3 Melanoma or squamous cell carcinoma pathology.

4.4. Interventions

Several risk factors will be monitored in patients with colorectal cancer and reported in the preoperative period, during the operation and in the post operative period, those risk factors are already established in literature.

These was done in two groups of patients:

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

difference in reporting and response between retrospective and prospective groups,

In the preoperative period the following will be monitored:

1. Tumor location.
2. Levels of CEA (carinoembryonic antigen) in the serum.

Intraoperatively the following risk factors will be monitored.

1. Intraoperative blood transfusion.
2. Intraoperative tumor perforation.
3. Quality of total mesorectal excision (TME) in cases of cancer rectum.

Postoperatively the following will be reported (mainly in the final histopathological examination report).

1. Tumor grade.
2. Intralymphatic and intravascular tumor invasion.
3. Non nodal tumor deposits (TDs).
4. Circumferential tumor margins.
5. Number of lymph nodes dissected with cut off point at 12 LNs and the percentage affected (lymph node ratio LNR).
6. Number of apical lymph nodes dissected.
7. Type of advancing margin of the tumor (infiltrative vs. pushing).
8. Genetic factors K-ras gene or others.

All these risk factors are to be reported to the treating oncologist for the difference in the management plan pre and postoperatively.

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 (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

5. Results

5.1. Reporting of the risk factors

From 664 old and 66 new cases of colorectal cancer, the reporting of above-mentioned risk factors is shown in Table 1.

5.2. Difference in reporting of risk factors between retrospective and prospective groups

The statistical difference significance between reporting of risk factors in both groups (retrospective and prospective) was calculated using Chi-Square. All statistical calculations were done using computer program SPSS [12] (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows. This is shown in Table 2.

6. Discussion

It is shown from Table 1 that the reporting of most risk factors was inadequate; also there was marked improvement of reporting in the prospective cases regarding preoperative CEA, intra operative blood transfusion, intraoperative tumor perforation, quality of TME, tumor grade and non-nodal T.Ds in which P-value were <0.0001 in all (look Table 2).

Many studies in the last few years have discussed the staging of colorectal cancer and its impact on the prognosis. A North American distinguished group of gastrointestinal pathologists have concluded that: *The 6th edition of the TNM classification fails to meet many of the challenges posed by the realities of modern cancer management*. Other limitations of the 6th edition of TNM staging that were reported by this group are failure of separating Stage 4a (involvement of adjacent organs) from 4b (transperitoneal spread) and the disappearance of specifically named lymph nodes [13].

In an editorial by Najiub Haboubi in 2011, he advised to combine TNM with the old and tried Duke's system, This was due to the inability of the TNM to incorporate the apical L.Ns involvement in the staging which in his point of view is a necessary factor when considering prognosis [14].

The use of TNM system alone may not be enough to plan the treatment protocol. As it was found that some risk factors contribute markedly to prognosis. The treating physicians may not be alert to the importance of reporting these associated risks, while others may not feel the importance of mentioning its presence as they may feel that it does not contribute to the treatment strategy as they are not included in the current TNM staging system [3].

Lim SB et al., in 2010 stated that the TNM classification, in its present status, does not address the other prognostic risk factors proved by reported evidence-based research in the field such as intralymphatic and intravascular deposits, where Lymphovascular invasion-positive tumors metastasized more often to the systemic lymph nodes ($P < 0.001$) [15].

Although the TNM staging system provides the essential prognostic information in determining the management of rectal cancer, it does not incorporate any data on other important prognostic

Table 1
Number and percentage of reporting of risk factors in both retrospective and prospective groups.

Risk factor	Retrospective cases (n = 644)		Prospective cases (n = 66)	
	Reported	Non reported	Reported	Non reported
1-Pre-operative CEA	272 (40.97%)	392 (59.03%)	46 (69.69%)	20 (30.31%)
2-IOBT	20 (3%)	644 (97%)	66 (100%)	0
3-IOTP	176 (26.5%)	468 (73.5%)	66 (100%)	0
4-Grade	455 (68.52%)	209 (%)	64 (96.96%)	2 (3.03%)
5-LNR	547 (82.37%)	117 (17.63%)	64 (96.96%)	2 (3.03%)
6-Non-nodal T.Ds	48 (7.228%)	616 (92.772%)	16 (24.24%)	50 (75.75%)
7-LVI	259 (39%)	405 (61%)	27 (41%)	39 (59%)
8-K-ras mutation	48 (7.23%)	616 (92.77%)	1 (1.56%)	65 (98.4%)
9-Apical L.Ns	23 (3.46%)	641 (96.54%)	5 (7.58%)	61 (92.42%)
10-Infiltrative vs pushing	477 (71.83%)	187 (28.17%)	58 (87.8%)	8 (12.1%)
11-circumferential tumor margins	306 (46.08%)	358 (53.92%)	54 (81.81%)	12 (18.15%)
12-Quality of TME (n of rectum cases = 282 & 30)	107 (37.95%)	175 (62.05%)	30 (100%)	0

Table 2
Statistical Difference in reporting between retrospective and prospective groups.

Risk factor	X^2	X^2 (Yates)	P-Value (df = 1)	P (Yates)
1-Pre-operative CEA	20.159	19.008	<0.0001	<0.0001
2-IOBT	534.358	534.006	<0.0001	<0.0001
3-IOTP	140.717	137.501	<0.0001	<0.0001
4-k-ras gene mutation	3.130	2.284	0.077	0.131
5-Non nodal T.Ds	21.725	19.650	<0.0001	<0.0001
6-Grade	23.638	22.274	<0.0001	<0.0001
7-Apical L.Ns	2.752	1.75	0.09	0.186
8-Lymphovascular invasion	0.091	0.029	0.763	0.8651
9-Lymph node ratio	9.366	8.327	0.002	0.004
10-Circumferential tumor margins.	30.668	29.255	<0.0001	<0.0001
11-Infiltrative vs pushing margins	7.891	7.093	0.005	0.008
12-Quality of Total meso rectal excision (TME)	42.398	39.916	<0.0001	<0.0001

factors such as circumferential radial margin (CRM) in its staging algorithm. A positive circumferential tumor margins (defined as a margin <1 mm) is highly associated with an increased risk of Local recurrence and decreased survival [16].

A TME in the mesorectal plane should offer a low risk of local recurrence (of about 4%–8%). F.J Fleming and J.R.T Monson suggest that conventional long course chemoradiation would represent overtreatment for patients with stage II/III rectal cancer and that it reasonable to go straight to TME [17].

Moreover the latest version of NCCN guidelines states that the grade of the cancer, state of radial margins, Lymphovascular invasion, perineural invasion and other risk factors should be reported [18]:

This continuous debate regarding the efficacy of the TNM and the need to combine it with other staging systems requires a major change in the TNM to accommodate this continuously expanding list of risk factors that have a great impact on the prognosis.

In this study, We suggest the addition of letter F to the TNM to be TNMF to be this change. The addition of this letter "F" to the TNM will give both the treating surgeon and oncologist an extra category to report all these prognostic risk **factors** in their treatment plan.

7. Conclusion and recommendations

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.

Ethical approval

It was approved by ethical committee of Faculty of medicine, Cairo university.

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Author contribution

1- Ahmed Farag Ahmed Farag is the first and main author and the idea of the research was his idea. He supervised all the steps.

2- Mohamed Yehia Elbarmelgi is the main researcher who collected the data, made the statistics and write the initial and final revised Manuscript.

3- Hamdy A Azim and Ahmed A Abozeid shared the data collection and supervision.

4- Abdrabou N Mashhour shared in data collection, doing the statistics and revision of the final manuscript.

Conflicts of interest

No conflicts of interest.

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