Impact of Molecular Tumor Board on the Clinical Management of Patients With Cancer

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PURPOSE Multidisciplinary molecular tumor boards (MTBs) help in interpreting complex genomic data generated by molecular tumor profiling and improve patients' access to targeted therapies. The purpose of this study was to assess the impact of our institution's MTB on the clinical management of patients with cancer.

METHODS This study was conducted at a tertiary cancer center in India. Cases to be discussed in the MTB were identified by molecular pathologists, scientists, or oncologists. On the basis of the clinical data and molecular test reports, a course of clinical management was recommended and made available to the treating oncologist. We determined the proportion of patients who were recommended a change in the clinical management. We also assessed compliance of the treating oncologists with MTB recommendations.

RESULTS There were 339 discussions for 328 unique patients. The median age of the cohort was 54 years (range 17-87), and the majority of the patients were men (65.1%). Of 339 cases, 133 (39.2%) were recommended continuation of ongoing therapy while the remaining 206 (60.7%) were recommended a change in clinical management. Compliance with MTB recommendations for a change in clinical management was 58.5% (79 of 138 evaluable cases). Compliance and implementation for MTB's recommendation to start a new therapy in 104 evaluable cases were 60.5% and 44.2%, respectively. A total of 248 biopsies had at least one actionable mutation. A total of 646 mutations were identified in the cohort, with *EGFR* being the most frequently altered gene.

CONCLUSION MTBs help in interpreting results of molecular tests, understanding the significance of molecular abnormalities, and assessing the benefits of available targeted therapies and clinical trials in the management of patients with targetable genetic alterations.

INTRODUCTION

As conventional chemotherapy affects both cancerous and noncancerous cells, its use is associated with side effects and general cytotoxicity.[1] Therefore, the focus of drug development has shifted to the discovery of novel therapeutic targets that can be exploited in the pursuit of precision medicine.[2] Majority of tumors are driven by oncogenic mutations that can be targeted with genetically matched therapies. Molecular diagnostic techniques, such as the next-generation sequencing (NGS), provide insights into the underlying disease biology and can help improve treatment outcomes through guiding the use of targeted therapies.[3] A classic example of this approach is the use of tyrosine kinase inhibitors (TKIs) in the treatment of epidermal growth factor receptor (*EGFR*)–mutated non–small-cell lung cancer (NSCLC).[4]

The increasing accuracy and speed and decreasing cost of NGS have led to the generation of an enormous quantity of genomic data, expanding our knowledge about the molecular landscape of cancer.[5,6] Moreover, the number of available targeted therapies is on the rise.[7] This has prompted the development of novel and innovative trial designs that attest to the efficacy and safety of novel targeted therapies.[6]

Molecular tumor profiling is being implemented in several cancer centers to select eligible candidates for targeted therapy. As a result, treating oncologists often face challenges such as interpreting the complex genomic data and assessing benefits of available clinical trials and off-label use of drugs. The complexity associated with the delivery of targeted therapies has prompted the creation of multidisciplinary molecular tumor boards (MTBs).[7-9] These are forums comprising members with specialties in oncology, radiology, surgery, pathology, molecular biology, informatics, etc held to discuss the multidisciplinary management of patients with cancer.[10] We started the MTB at our center to provide better care to our patients. Here, we

CONTEXT

Key Objective
What was the impact of discussion in the institutional molecular tumor board (MTB) on the clinical management of patients with cancer?

Knowledge Generated
The MTB discussion led to a recommendation to change management in 63.4%. Compliance with MTB recommendations for a change in clinical management was 58.1%.

Relevance
Multidisciplinary MTBs help improve access to targeted therapies and optimize the clinical management of patients with targetable genetic alterations.

report our experience with patients who underwent genomic testing and whose cases were discussed in our MTB. We retrospectively evaluated the impact of MTB recommendations on the therapeutic decision-making of the treating oncologists in our center.

METHODS

Study Details

This is a retrospective analysis of the data from all the cases discussed in the MTB of Tata Memorial Hospital, a tertiary cancer center in India, between May 22, 2019, and March 24, 2021. The MTB comprised a multidisciplinary team of medical oncologists, surgical oncologists, pathologists, bioinformaticians, molecular biologists, and molecular pathologists who convened once a week. Cases discussed in the MTB were identified through various sources including molecular pathologists/scientists who had performed the tests for in-house patients, treating clinicians who requested discussion of various molecular reports, or outside reports that were sent for expert opinion. Molecular tests as recommended by the treating oncologists were performed either on formalin-fixed paraffin-embedded tumor tissue, lymph node biopsy, blood, pleural fluid, or other bodily fluid. NGS was the most common test, followed by real-time polymerase chain reaction (RT-PCR). For samples tested by NGS, genomic alterations were identified using the computational best practices pipeline, WaterHose-ClinOme.[11-13] Those with targetable alterations were recommended suitable therapy on the basis of data available from various trials conducted globally for patients with genomic alterations while considering the availability and affordability of drugs in our setting. Considering the clinical data and molecular test reports, recommendations were made for each patient either for continuation of ongoing therapy, starting a new therapy, performing a new diagnostic test, or consideration of enrollment in a clinical trial. For all the cases, recommendations made by the MTB were conveyed to the treating clinicians and patients by documentation in electronic medical record and were recorded in a database maintained in Microsoft Excel. This study did not require ethical approval because of its noninterventional nature; patient consent was not required as only deidentified data were analyzed and reported. The study was performed in accordance with the ethical standards of the institutional committee on human experimentation and the Declaration of Helsinki. There was no funding involved in this study.

Study Participants and Data Collection

Patients receiving or planned for systemic treatment at our hospital who underwent molecular testing on biopsied tissues or bodily fluids during the study period and whose cases were discussed in the MTB were included. Similarly, patients receiving or planned for systemic treatment at other centers who underwent molecular testing and whose reports were sent to our MTB for expert opinion were included in the study. For all cases discussed in the MTB, data including demographics, histopathological findings, and clinical course of the disease were presented by the clinician and entered in the MTB database. Results of molecular tests were presented by the molecular pathologist/scientist, followed by a discussion and interpretation by all the members of the multidisciplinary MTB. These details and the final MTB recommendations were also entered in the database. These data were extracted from the database, and the electronic medical records were then accessed to determine compliance with MTB's recommendations and the subsequent clinical course. The workflow for referral and evaluation of cases in the MTB is depicted in Figure 1.

Study End Points

The primary end point was to assess the change in clinical management, defined as compliance with at least one of the following MTB recommendations:

1. Starting a new targeted therapy
2. Performing a new molecular diagnostic test
3. Consideration for enrollment of the patient in a clinical trial

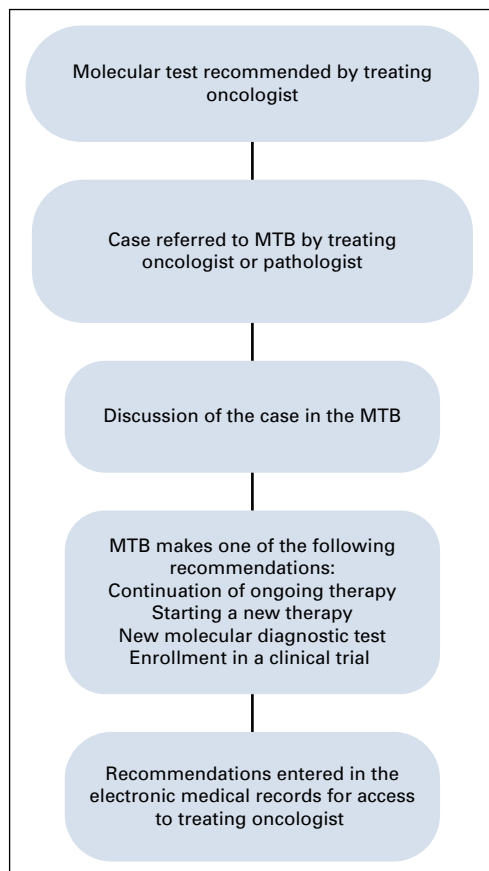Secondary end points included determination of the following:

FIG 1. Work flow for referral to and evaluation of cases in MTB. MTB, molecular tumor board.

1. Proportion of patients in the cohort with at least one actionable mutation
2. Proportion of patients for whom a change in the clinical management was recommended and proportion of patients in whom these recommendations were complied with by the treating oncologist.
3. Implementation rate for the recommendation of starting a new therapy

Definitions

1. The MTB's recommendation was considered to be complied with when the treating oncologist proposed a treatment plan in accordance with the MTB's advice.
2. The MTB's recommendation to start a new therapy was considered to be implemented if the patient was administered the new therapy recommended by the MTB.

Statistical Analysis

Sample size calculation was not performed for this study; all cases discussed in the MTB during the study period were included. Patient characteristics have been reported using descriptive statistics. Values are reported as absolute numbers and simple percentages. Median has been reported wherever applicable.

RESULTS

Cases Discussed in MTB

There were 339 discussions for 328 unique patients in the MTB of our center during the study period. The median age of the cohort was 54 years (range 17-87), and majority of the patients were men (65.1%). Demographic details of these patients are presented in Table 1; for two patients treated at other centers, details of tumor histology were not available. The commonest primary tumor site was the lung (75.8%), and adenocarcinoma was the most common histology (71.8%). In all, 291 (85.8%) biopsies were tested by NGS, 37 (10.9%) by RT-PCR, and 5 (1.4%) by immunohistochemistry and fluorescent in situ hybridization.

A total of 646 mutations were detected in 339 biopsies, including insertions/deletions/base substitutions, rearrangements, amplifications, and losses. The relative proportion of mutations detected in our cohort is depicted in Figure 2.

A total of 248 biopsies had at least one actionable mutation. The most frequently altered gene was *EGFR*, followed by *ALK*, *TP53*, and *KRAS*. The relative proportion of alterations in various genes is presented in Table 2.

MTB Recommendations

On the basis of the presence or absence of actionable mutations in the biopsy, a recommendation was made by the MTB for clinical management of the disease. Of 339 cases discussed in the MTB, a recommendation to continue the ongoing therapy was made in 133 (39.2%), for starting a new therapy in 159 (46.9%), for performing a new molecular diagnostic test in 46 (13.5%), and for consideration of enrollment in a clinical trial in one (0.29%) case. Of the 133 cases in which the MTB recommended continuation of the ongoing therapy, in 50 (37.5%), there were no targetable mutations, in 33 (24.8%), the patient was already receiving a targeted agent, and in 36 (27.0%), either the use of a targeted agent approved for the same mutation in a different malignancy at disease progression after exhausting the standard lines of therapy (off-label use of a drug) or a new test at progression was recommended; in the remaining 14 (10.5%) cases, a new therapy was not recommended either because of the poor performance status of the patient or the lack of availability or affordability of an approved drug.

Compliance and Implementation of Recommendations

Of 159 cases in which the MTB recommended to start a new therapy, compliance with recommendations could be assessed in only 104; the remaining 55 cases were excluded either because the patient defaulted (34), was undergoing treatment at another center (15), or died before consideration of MTB's recommendation by the treating oncologist (6). Thus, of 104 cases, the recommendation to start a new therapy was complied with in 63 (60.5%) and implemented in 46 (44.2%). Similarly of 46 cases in which

TABLE 1. Demographic Details of Cases Discussed in the Molecular Tumor Board

Patient Characteristic	No. of Patients (%)
Age, years	
Median	54
Range	17-87
Sex	
Male	221 (65.1)
Female	118 (34.8)
Primary site	
Breast	5
Esophagus	9
Head and neck	17
Lung	257 (75.8)
Thyroid	5
Prostate	7
Unknown primary	3
Others[a]	36
Histology	
Adenocarcinoma	242 (71.8)
Poorly differentiated carcinoma	11
Squamous cell carcinoma	21
Sacromatoid carcinoma	5
Small-cell carcinoma	7
Others[b]	51

[a]Adrenal gland, anal canal, appendix, bladder, bones, bronchus, colon, connective tissue, gastroesophageal junction, gluteal region, kidney, malignant peripheral nerve sheath tumor, mediastinum, ovary, pancreas, retroperitoneum, skin, smooth muscle, soft tissue, testes, thymus, trachea, urethra, vagina, and vulva.

[b]Adenoid cystic carcinoma, adenosquamous carcinoma, adrenal cortical carcinoma, anaplastic carcinoma, biphasic mesotheliomas, borderline serous tumor, carcinoma, chordoma, esthesioneuroblastoma, fibroblastic tumor, fibromatosis, high-grade sarcoma, hurthle cell tumor, inflammatory myofibroblastic tumor, invasive lobular triple-negative breast cancer, liposarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, melanoma, medullary carcinoma, mesothelioma, mucoepidermoid carcinoma, neuroendocrine carcinoma, nonkeratinizing carcinoma, osteosarcoma, papillary thyroid carcinoma, pleomorphic carcinoma, renal cell carcinoma, primitive neuroectodermal tumor, salivary duct carcinoma, seminoma, sarcoma, thymoma, and yolk sac tumor.

the MTB recommended a new molecular diagnostic test, the compliance with the MTB recommendation could be assessed in 33 cases; the remaining 13 cases were excluded either because the patient defaulted (10), was undergoing treatment at another center (two), or died before consideration of the MTB's recommendation by the treating oncologist (one). Thus, of 33 cases, the recommendation to perform a new test was complied with in 15 (45.4%). Only one patient was recommended enrollment in a clinical trial, and this recommendation was complied with

by the treating oncologist (Fig 3). Thus, the overall compliance with MTB's recommendations for a change in the clinical management was 58.5% (79 of 138 cases).

Majority (257) of the cases discussed in our MTB were of lung cancer. For a total of 257 cases of lung cancer, there were 101 (39.2%) recommendations for continuation of ongoing therapy, 122 (47.4%) recommendations for starting a new therapy, 34 (13.2%) recommendations for a new molecular diagnostic test, and no recommendations for enrollment in a clinical trial. An analysis of the recommendations made by the MTB for a change in the clinical management of patients with lung cancer and the compliance with these recommendations is depicted in Figure 4. Among those with lung cancer, 25 cases had an actionable *ALK* alteration of which ALK-directed treatment had already been started in 5 cases. Similarly, 92 cases had an actionable *EGFR* alteration of which EGFR-directed treatment had already been started in 19 cases.

DISCUSSION

Our study highlights the importance of multidisciplinary MTBs. We observed that of the 339 cases discussed in our institution's MTB, a recommendation to modify the existing course of clinical management was made in 206 (60.7%) cases. The fact that our MTB recommended a change in the clinical management in such a large proportion of cases emphasizes the significance of multidisciplinary MTBs in identifying candidates who could potentially benefit from targeted therapies. Moreover, the high level of compliance (58.5%) with the MTB's recommendations in our study indicates that the treating oncologists found the recommendations valuable.

Tafe et al reported the impact of the MTB on treatment decisions for 35 patients evaluated at the Dartmouth-Hitchcock Medical Center. It was observed that the MTB could recommend treatment with a targeted therapy in 56.3% of the patients.[14] Trivedi et al[15] in their study on the implementation and outcomes of the MTB at the Herbert-Herman Cancer Center reported that a genetically matched targeted therapy or enrollment in a clinical trial could be recommended in 81% of the patients. In our study, despite the presence of actionable genetic alterations in a significant proportion of cases (73.1%), the MTB recommended starting a new therapy (46.9%) or enrolling in a clinical trial (0.29%) in a relatively smaller proportion of cases. This could be due to the limited availability of clinical trials and molecular targeted therapies in the Indian setting.[16-18] In compliance with MTB's recommendation, one patient with esthesioneuroblastoma harboring an *NTRK1-NCAPD4* gene fusion was suggested enrollment in a clinical trial for larotrectinib by the treating oncologist; however, as the trial was being conducted at Singapore, the patient refused to comply with the recommendation. Moreover, although more than one third of our patients were not recommended any change in their clinical management, we believe that
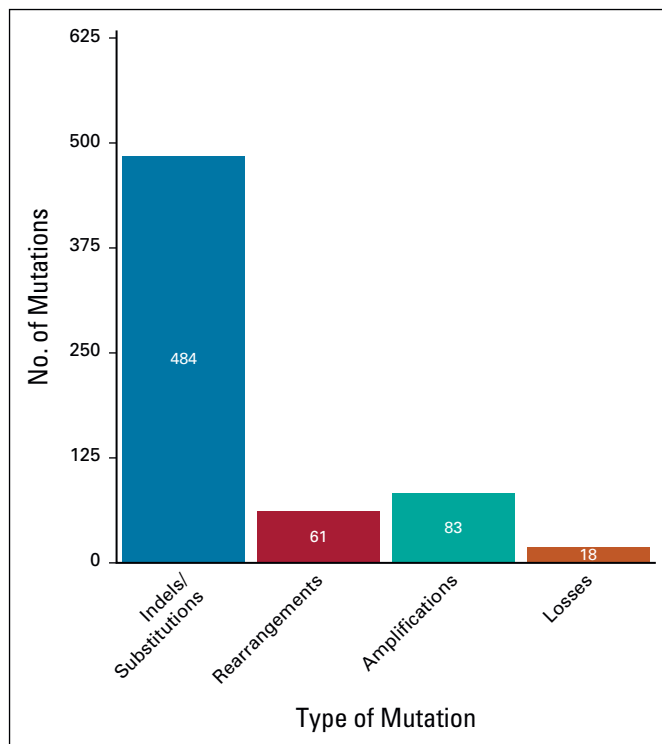
FIG 2. Proportion of the types of mutations observed in the study cohort.

TABLE 2. Frequently Altered Genes in the Cohort

Gene	No. of Alterations
EGFR	
Exon 19 del mutation	74
Exon 21 L858R	25
Exon 20 insertion	15
Exon 20 T790M	21
Exon 20 S768I	7
Exon 21 L861Q	5
Exon 18 G719X	12
Other mutations[a]	15
Amplification	8
Rearrangement	1
ALK	
Mutation	12
Rearrangement	21
Amplification	12
KRAS	
G12C	10
G12D	11
G12V	3
Other mutations[b]	8
Amplification	1
TP53	59
ERBB2	24
PIK3CA	21
RET	20
Others	261

[a]c.2303_2311dup (p.Ser768_Asp770dup), c.2320G>A (p.Val774Met), c.2217_2234dup (p.Ile740_Lys745dup), c.2252C>T (p.Thr751Ile), c.2095C>T (p. Pro699Ser), c.2390G>C (p.Cys797Ser), c.252126A>C (p.Glu709Ala), c.2500G>T (p.Val834Lue), c.2336G>A (p.Gly779Asp), c.2248G>C (p.Ala750Pro), c.2174C>T (p. Thr725Met), EGFRvIII.

[b]c.34G>A (p. Gly12Ser), c.38G>A (p. Gly13DAsp), c35G>C (p.Gly612Ala), c.183A>C (p.Gln61His).

they benefitted from the discussion in the MTB as it helped establish the clinical relevance and impact of the observed genetic mutations and explore alternative anticancer and other therapies when approved targeted agents were not available. Additionally, in our study, the recommendation for starting a new therapy had better compliance (60.5%) than that for performing a new test (45.4%). This can be attributed to the limited availability of the biological sample for testing and the high cost of some of the recommended tests, such as NGS.

In our cohort, *EGFR* was the most frequently altered gene. Several first-, second-, and third-generation EGFR-TKIs are commercially available in India. Besides *EGFR*, a large proportion of genetic alterations in our cohort was observed in *ALK*, *KRAS*, *ERBB2*, *PIK3CA*, and *BRAF* genes. However, the availability of targeted therapies directed at these genes in India is limited. The MTB helped improve the access to drugs such as dabrafenib, trametinib, and lorlatinib by recommending their procurement on compassionate basis.[19] It also helped improve access to poziotinib for patients with NSCLC harboring exon 20 insertions.

Our MTB helped treating oncologists identify new uses for approved drugs beyond their original standard indications. One such drug was sorafenib, a kinase inhibitor approved for the treatment of renal cell and hepatocellular carcinomas. A patient with NSCLC harboring a *BRAF* non-V600E mutation was recommended sorafenib at disease progression after exhausting standard-line therapies.[20] In two patients with head and neck cancer harboring a *CDKN2A* mutation, repurposing sorafenib was recommended at disease progression.[21] In another patient with NSCLC harboring a *KRAS* mutation, sorafenib was recommended in later lines.[22] Treatment with erlotinib, an oral TKI approved for NSCLC, was recommended for a female patient with triple-negative breast adenocarcinoma harboring an *EGFR* exon 21 L861Q mutation.[23] The MTB also recommended therapy with selpercatinib, a drug approved for the treatment of lung and thyroid cancers with *RET* gene mutations, in a female with skene gland adenocarcinoma harboring a *TBP-RET* fusion.[24]

FIG 3. Flow chart for inclusion of patients. MTB, molecular tumor board.
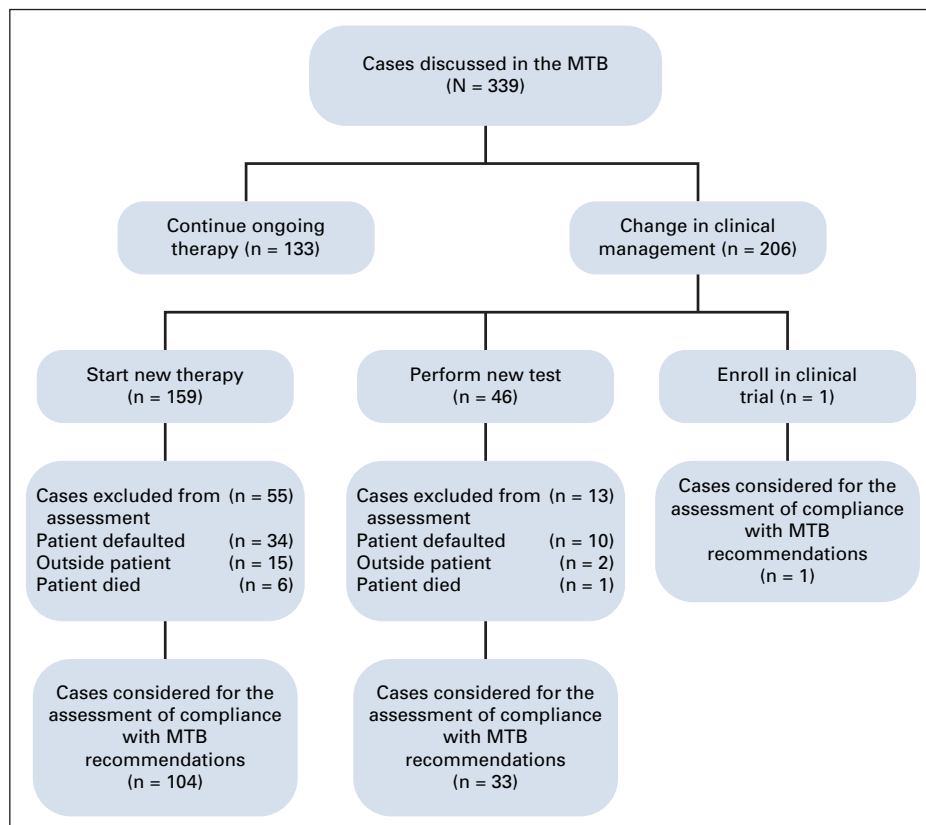
Nine patients discussed in the MTB had concomitant *EGFR* and *ALK* mutations. There are conflicting reports about the efficacies of ALK- and EGFR-directed therapies in such cases. Moreover, there are limited data on the concomitant use of EGFR and ALK inhibitors in such patients.[25] For five of nine patients, our MTB recommended dual EGFR- and ALK-directed therapies, with close monitoring for toxicities. For the remaining four cases, either ALK- or EGFR-directed

FIG 4. Molecular tumor board recommendations for change in clinical management and their compliance in patients with lung cancer.

therapies were recommended after progression on earlier lines of therapy, on the basis of the specific types of mutations and patient characteristics.

Studies suggest that targeting the beta-catenin pathway could provide a novel strategy to prevent or overcome resistance to EGFR-TKIs. Kato et al[26] reported that overall survival and progression-free survival of patients who received therapeutic regimens recommended by the MTB were better than the overall survival and progression-free survival of those who received treatment regimens of the physicians' choice.

Recommendations of the MTB can vary according to the molecular tests performed. However, in our study, about 86% of the specimens were tested by NGS. Immunohistochemistry and fluorescent in situ hybridization together were performed for < 1.5% of specimens, primarily for the detection and confirmation of *ALK/ROS1*-positive or *HER2/neu*-expressing tumors. Moreover, RT-PCR was performed for 10% specimens, and these were predominantly cases of lung adenocarcinoma for which an RT-PCR is a highly sensitive and widely accepted detection method for *EGFR* mutations. We, therefore, believe that for cases not analyzed by NGS, the MTB's recommendation would not have differed from the current recommendations had an NGS been performed. This is because samples not analyzed by NGS were analyzed
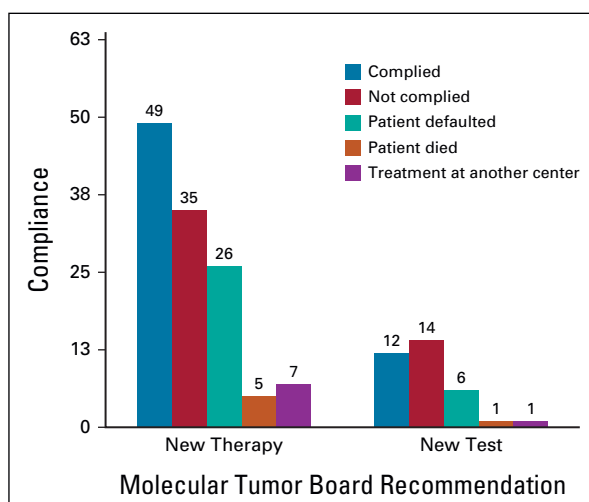
by the recommended gold standard techniques relevant to the cancer type and/or type of genetic alteration.

Our study had its limitations. First, it was a retrospective study with a heterogeneous patient population. Second, patient outcomes after implementation of the MTB recommendation were not evaluated, and all the cases were not rediscussed in the MTB at a later time point. Third, patients whose cases were discussed in the MTB but were receiving treatment at other centers were not followed up. Finally, cases discussed in the MTB were only those that were referred by the treating oncologist or pathologist; a comprehensive discussion of all cases with molecular mutations was not performed. Therefore, it is likely that only cases with less common mutations were referred for discussion while those with more common and well-known mutations, such as the *EGFR*-sensitizing mutations, in the first-line setting were managed by the treating oncologist without referral to the MTB. Additionally, it was observed that compliance with MTB recommendations was higher among oncologists who were also members of the MTB.

To the best of our knowledge, ours is the largest study from India to assess the impact of MTB on clinical management of patients with cancer and adds to the growing body of literature that highlights the need for such multidisciplinary forums to rationally evaluate the molecular profile of tumors and improve patients' access to targeted therapies. In future, larger prospective studies are warranted to assess the clinical outcomes of patients receiving MTB-guided treatment. Therefore, there is a need to create more awareness about the usefulness of MTBs and to improve the follow-up from MTB to ensure the implementation of its recommendations in clinical practice.

In conclusion, discussion in our institution's MTB resulted in a recommendation for change in clinical management in 206 of 339 cases. MTBs help in interpreting the results of molecular tests, understanding the significance of various molecular abnormalities, and assessing the benefits of the available targeted therapies and clinical trials in the clinical management of patients with targetable genetic alterations in their tumors.

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