Approach to Diagnosis of Salivary Gland Tumors and Use of Ancillary Studies

Dr. Neha Mittal

Professor and Pathologist

Tata Memorial Centre, Mumbai

Salivary Gland Tumors

Diagnostic challenges:

- These tumors are relatively uncommon
- Include morphologically diverse tumors
- Overlapping morphological features
- Complex morphology including
  - Hybrid tumors
  - Benign tumors progressing to malignancy
  - High grade transformation in low grade tumors

Salivary Glands: Types and Location

Major Salivary Glands

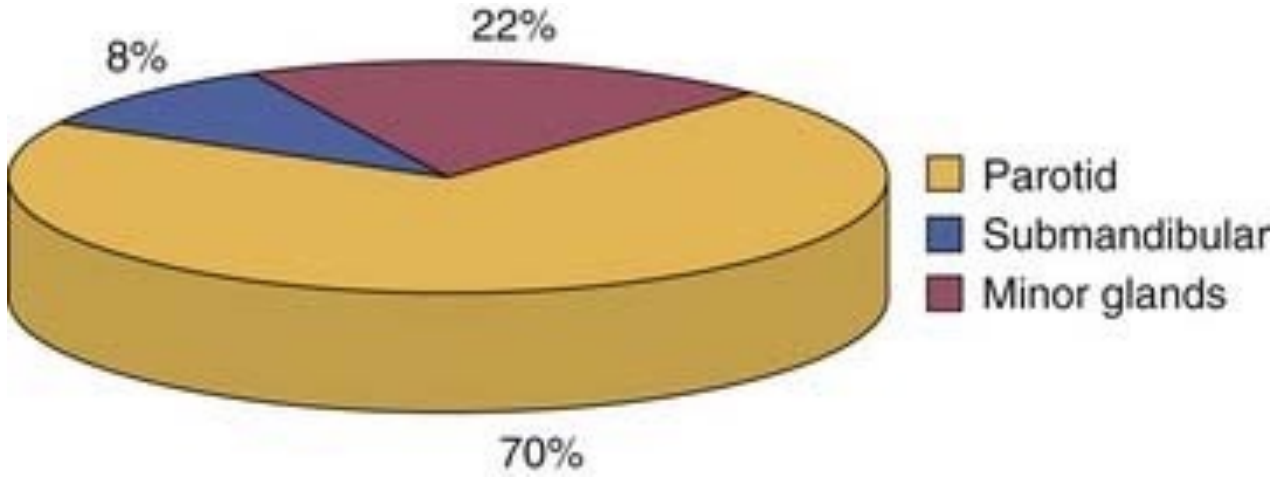
- Parotid
- Submandibular
- Sublingual

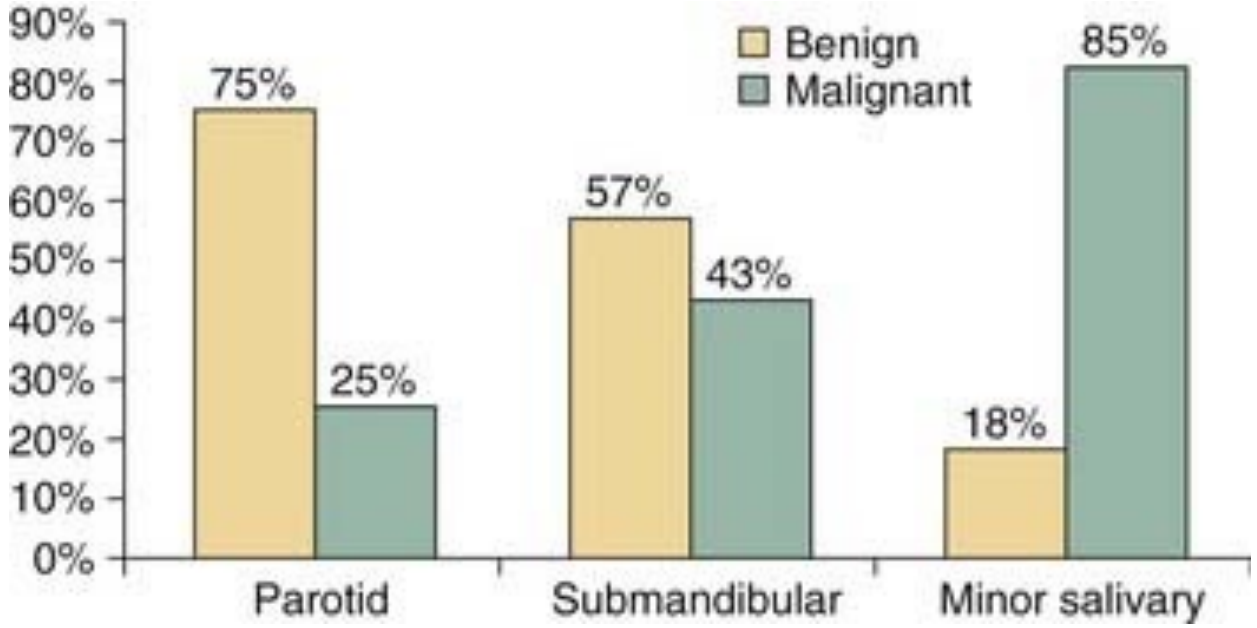
Minor Salivary Glands

- Buccal mucosa
- Lips
- Tongue
- Floor of mouth
- Palate and uvula
- Peritonsillar area
- Paranasal sinuses
- Larynx, trachea, bronchi

- Global incidence: 0.4 - 13.5 cases per 100,000 population
- About 0.3% of all malignancies and 6% of head neck malignancies
- Incidence of malignant and benign tumors varies according to the location of the tumor

Location of tumor is important





What is the role of Pathologist

- FNAC
- Biopsy
- Frozen section
- Resection Specimen

Role of FNAC

First-line diagnostic approach for triaging the case:

- Non-neoplastic and inflammatory: Conservative / medical treatment
- Neoplasms: All benign and malignant neoplasms needed to be removed surgically*
- Malignant neoplasms*: Low-grade vs. high-grade cancers
  - Low-grade cancers – Surgical resection with adequate margins
  - High-grade cancers – Surgical resection with adequate margins + regional node dissection and/or adjuvant chemotherapy/radiotherapy

****Except Lymphoma (no surgery, requires chemotherapy)***

Received: 8 August 2018 | Revised: 19 January 2019 | Accepted: 19 February 2019

DOI: 10.1002/hed.25732

WILEY

ORIGINAL ARTICLE

The Milan System for Reporting Salivary Gland Cytopathology—Proposed modifications to improve clinical utility

Francesco Mazzola MBBS[1,2] | Ruta Gupta MBBS, MD, FRCPA[3,4] | Peter P. Luk MBBS[3] | Carsten Palme MBBS (Hons.)[2,3] | Jonathan R. Clark MBBS (Hons.)[2,3] | Tsu-Hui (Hubert) Low MBBS (Hons.)[2,3]

TABLE 1 The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) categories

Category	Definition
I	Non-diagnostic
II	Non-neoplastic
III	Atypia of Undetermined Significance (AUS)
IV	Neoplasm
IVa	Neoplasm: Benign
IVb	Neoplasm: Salivary gland neoplasm of Uncertain Malignant Potential (SUMP)
V	Suspicious for malignancy
VI	Malignant

TABLE 4 Modified Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) categories

Category	Definition
I	Non-diagnostic
II	Non-neoplastic
III	Neoplasm: Benign
IV	Salivary Lesion of Uncertain Malignant Potential (SLUMP)
V	Suspicious for malignancy
VI	Malignant neoplasm
VIa	Low-grade salivary gland neoplasm
VIb	High-grade salivary gland neoplasm or other malignant neoplasms
VII	Haematologic malignant neoplasm

Proposal for revision of the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) classification.

MazzolaF, GuptaR, Luk PP, Palme C, Clark JR, Low T-H. The Milan System for Reporting Salivary Gland Cytopathology—Proposed modifications to improve clinical utility. Head & Neck. 2019;41:2566–2573. https://doi.org/10.1002/hed.25732

Milan System for Reporting Salivary gland cytology

- Category I - Non-diagnostic
- Category II - Non-neoplastic
- Category III - AUS (Atypia of undetermined significance)
- Category IVA - Neoplasm-Benign
- Category IVB - Neoplasm-SUMP (Salivary gland lesion of uncertain malignant potential)
- Category V - Suspicious for malignancy
- Category VI - Malignant

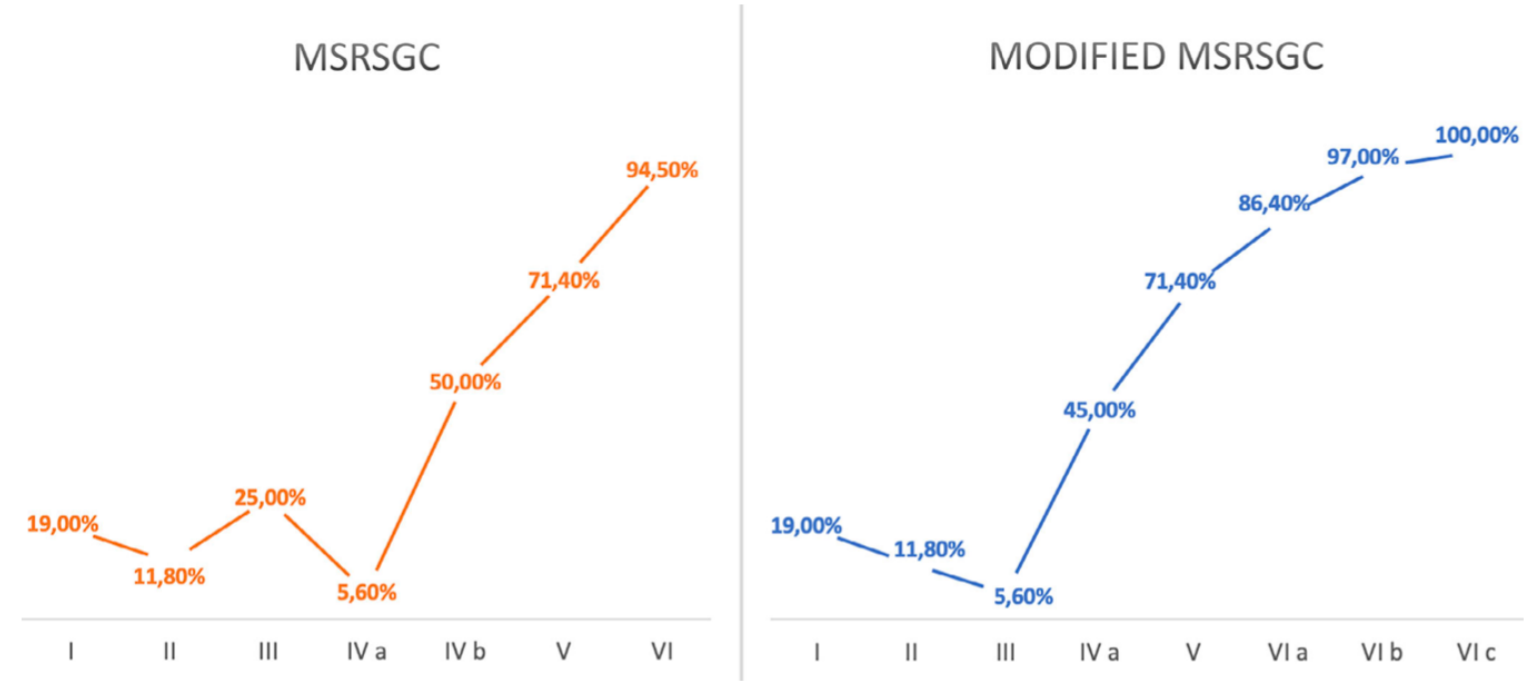


FIGURE 1 ROM per category in standard and modified Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) classification. ROM: Risk of malignancy [Color figure can be viewed at wileyonlinelibrary.com]

Biopsy of Salivary gland lesions

- Usually obtained for mucosa-based (minor salivary gland) lesions

ASCO guidelines
Recommendation 1.5.
Providers should perform a tissue biopsy (either fine needle aspiration biopsy [FNAB] or core needle biopsy [CNB]) to support distinction of salivary gland cancers from nonmalignant salivary lesions (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Role of frozen section

- Controversial, although frequently used to find out
  - Whether the lesion is neoplastic or non-neoplastic
  - Benign or malignant
  - Low grade vs. high grade
  - Completely resected or not

Head and Neck Pathology (2021) 15:859–865
https://doi.org/10.1007/s12105-021-01306-8

ORIGINAL PAPER

Is there a Role for Frozen Section Evaluation of Parotid Masses After Preoperative Cytology or Biopsy Diagnosis?

R. G. Pastorello[1] · E. F. Rodriguez[2] · B. A. McCormick[3] · V. F. Calsavara[4] · L. C. Chen[3] · M. A. Zarka[3] · A. C. Schmitt[3]

Received: 11 December 2020 / Accepted: 6 February 2021 / Published onli Febru 1

Bias alert!!

- 76 patients (45.5%) had both FNA and FS
- In 35 cases deemed as benign preoperatively, three 6%) ere reclassified as malignant on FS
- Out of 18 lesions reported as malignant on FNA, four (22.2%) were interpreted as benign on FS
- Compared to FNA, FS was able to provide a definitive diagnosis in all five ND cases and in 61.1% (11/18) of indeterminate tumors.
- Intraoperative assessment provided a relative increase of 33.3% in specificity and 38.5% in positive predictive value when compared to preoperative FNA.

Resection specimen: Contents of report

- Tumor site
- Tumor dimensions
- **Histologic type**
- Histologic grade (Low vs High)
- Extent of invasion
- LVI and PNI
- Completeness of resection: Status of margins
- Pathologic stage: TNM stage

Salivary Gland Tumors: Histologic Types

WHO 2022

Non-neoplastic epithelial lesions

- Nodular oncocytic hyperplasia
- Lymphoepithelial sialadenitis
- ***Benign epithelial tumours***
- Pleomorphic adenoma
- Basal cell adenoma
- Warthin tumour
- Oncocytoma
- Salivary gland myoepithelioma
- Canalicular adenoma
- Cystadenoma of the salivary glands
- Ductal papillomas
- Sialadenoma papilliferum
- Lymphadenoma
- Sebaceous adenoma
- Intercalated duct adenoma and hyperplasia
- Striated duct adenoma
- **Sclerosing polycystic adenoma**
- **Keratocystoma**

Mesenchymal tumours specific to the salivary glands

- Sialolipoma

- ***Malignant epithelial tumours***
- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Acinic cell carcinoma
- Secretory carcinoma
- **Microsecretory adenocarcinoma**
- Polymorphous adenocarcinoma
- Hyalinizing clear cell carcinoma
- Basal cell adenocarcinoma
- Intraductal carcinoma
- Salivary duct carcinoma
- Myoepithelial carcinoma
- Epithelial-myoepithelial carcinoma
- Mucinous adenocarcinoma
- **Sclerosing microcystic adenocarcinoma**
- Carcinoma ex pleomorphic adenoma
- Carcinosarcoma of the salivary glands
- Sebaceous adenocarcinoma
- Lymphoepithelial carcinoma
- Squamous cell carcinoma
- Sialoblastoma
- Salivary carcinoma NOS and emerging entities

Changes in WHO classification since 2017

New entities

Secretory carcinoma: First described in 2010. Formerly known as mammary analogue secretory carcinoma (MASC)

Sclerosing polycystic adenosis

New names

Polymorphous adenocarcinoma: Formerly polymorphous low-grade adenocarcinoma

Intraductal carcinoma: Formerly low grade cribriform cystadenocarcinoma, low grade salivary duct carcinoma, salivary duct carcinoma *in situ*

Poorly differentiated carcinoma: Includes undifferentiated carcinoma, large and small cell neuroendocrine carcinoma

Clarifications, changes

- Adenocarcinoma NOS: Includes cystadenocarcinoma, mucinous (cyst)adenocarcinoma, papillary cystadenocarcinoma
- Carcinoma ex-pleomorphic adenoma: Clarifications on diagnostic terminology: should explicitly state the histological type of malignant component
- Newer entities: NUT carcinoma, Adamantinoma-like Ewing sarcoma

Metastasizing pleomorphic adenoma :Moved from malignant category to a variant of benign pleomorphic adenoma

Sialadenoma papilliferum :Given its own category. No longer a “ductal papilloma”

Ductal papilloma: A single name for two variants: inverted ductal papilloma and intraductal papilloma

Lymphadenoma: A single category replacing sebaceous and non-sebaceous lymphadenomas. Sebaceous-type is regarded as a simple variant

Non-neoplastic epithelial lesions: New category, nodular oncocytic hyperplasia, lymphoepithelial sialadenitis, intercalated duct hyperplasia

Salivary Gland Tumors: Facts

- WHO classification describes 11 types of benign and 21 malignant tumors of epithelial origin of salivary glands
- Treatment decision is based on:
  - Stage of tumor (AJCC)
  - Location of tumor
  - Grade of tumor (Low or High)

The 5-year survival rate is 85-90% in low-grade tumors and 40% in high-grade tumors

Is it important to identify the histologic types of salivary gland tumors?

Low risk	High risk
Acinic carcinoma	Adenoid cystic carcinoma, solid and HGT
Low grade mucoepidermoid	High grade mucoepidermoid carcinoma
Epithelial-myoepithelial carcinoma	Salivary duct carcinoma
Polymorphous adenocarcinoma	Sebaceous and lymphadenocarcinoma
Clear cell carcinoma, NOS	Squamous cell carcinoma
Basal cell adenocarcinoma	Small cell carcinoma
LG cribriform cystadenocarcinoma	Lymphoepithelial carcinoma
Myoepithelial carcinoma, low grade	Myoepithelial carcinoma, high grade
Oncocytic carcinoma	Carcinosarcoma
Non-invasive (Intracapsular) Ca ex-PA	Invasive Ca ex-PA or high grade
Sialoblastoma	Large cell carcinoma
Adenocarcinoma, Low grade	Adenocarcinoma, high grade
Cystadenocarcinoma, low grade	Cystadenocarcinoma, high grade

HEAD AND NECK CANCER

original reports

Regression Derived Staging Model to Predict Overall and Disease Specific Survival in Patients With Major Salivary Gland Carcinomas With Independent External Validation

Natarajan Ramalingam, MS[1]; Shivakumar Thiagarajan, MS[1]; Nithyanand Chidambaranathan, MS[1]; Arjun Gurmeet Singh, MDS[1]; Devendra Chaukar, MS[1]; and Pankaj Chaturvedi, MS[1]

- Results show that combination of **tumor grade and histology** is an independent predictor of OS and DSS in salivary gland tumors and provides additional prognostic information along with AJCC category.

- Multiplicity or total absence of grading schemes and lack of consensus/structured reporting.

Salivary gland tumors in the era of precision medicine

Head & Neck Pathology consultations

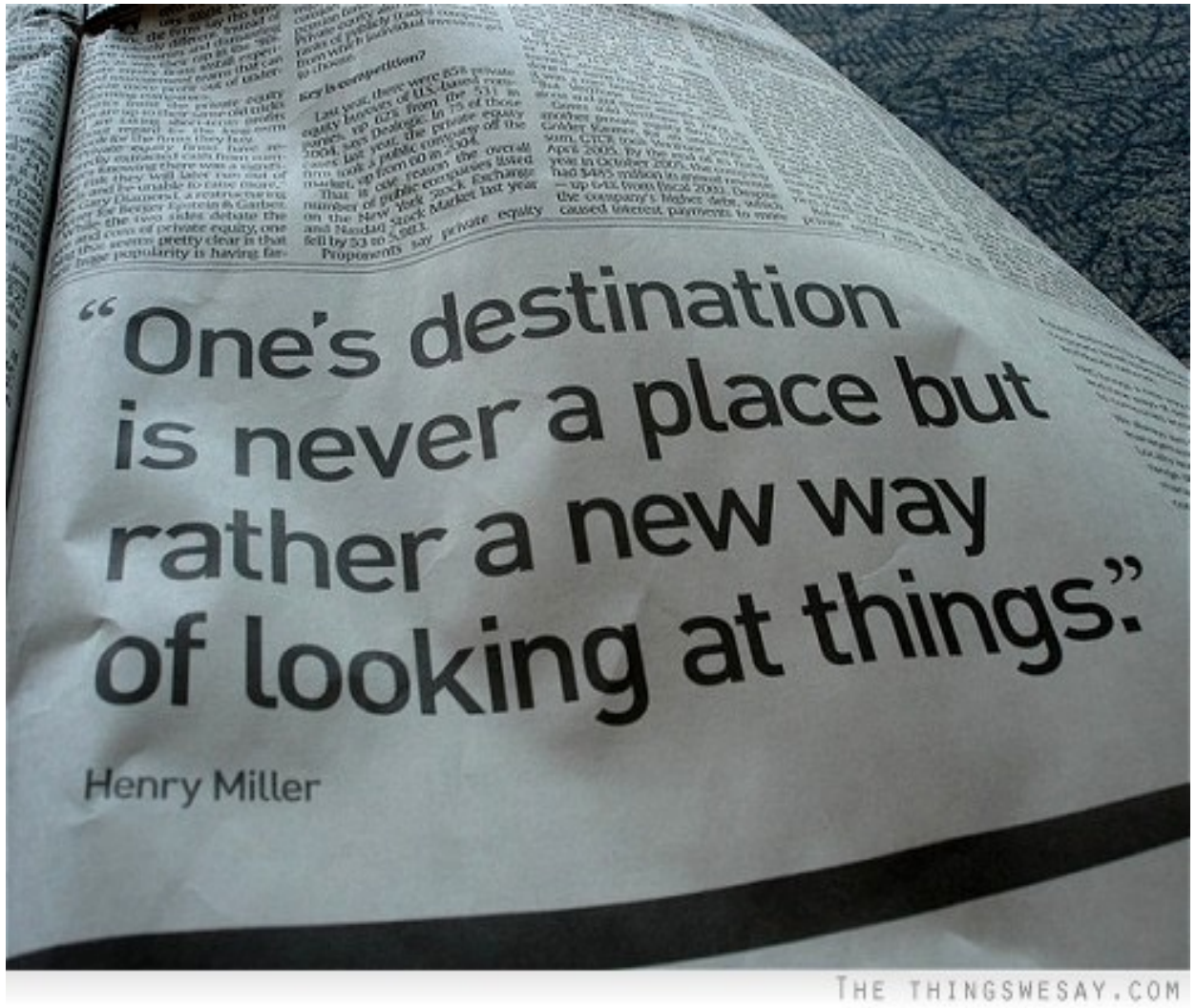
Salivary Gland Genetics

Tumor	Gene	Frequency
Pleomorphic adenoma	*PLAG1* (8q12) (70%) *HMGA2* (12q14-15) (20%)	Up to 90%
Basal cell adenoma	*CTNNB1* mutation	70-80%
Mucoepidermoid carcinoma	*CRTC1-MAML2* (*CRTC3*) t(11;19)(q21;p13)	80% (not grade associated)
Acinic cell carcinoma	t(4;9)(q13;q31) & *HTN3-MSANTD3* fusion	80% and 10%
Adenoid cystic carcinoma	*MYB-NFIB* (*MYBL1*) t(6;9)(q22-23;p23-24)	60-70%
Polymorphous adenocarcinoma	*ARID1A-PRKD1* (*PRKD2*, *PRKD3*) or *DDX3X-PRKD1*	20-50%
Salivary duct carcinoma	*TP53*, *HRAS*, *PIK3CA*, *PTEN* mutations; *ERBB2* amplification	90%
Secretory carcinoma	*ETV6-NTRK3* (*RET, MET*) t(12;15)(p13;q25)	>95%
Intraductal carcinoma	*NCOA4-RET* or *RET-TRIM27*	50%
Clear cell carcinoma	*EWSR1-ATF1* (*CREM*) t(12;22)(q13;q12)	90%

Acknowledgement

- Dr. Asawari Patil
- Dr. Munita Bal
- Dr. Swapnil Rane
- Dr. Katha Rabade
- Colleagues, Residents, Technicians, Tata Memorial Hospital and ACTREC
- Head Neck Disease Management group, Tata Memorial Centre

Thank you


"One's destination
is never a place but
rather a new way
of looking at things."
Henry Miller
THE THINGSWESAY.COM


WHEN YOU CHANGE THE WAY
YOU LOOK AT THINGS
THE THINGS YOU LOOK AT
CHANGE