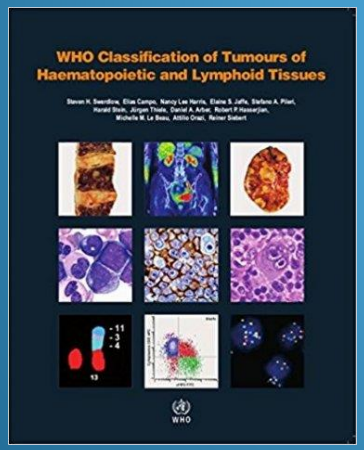
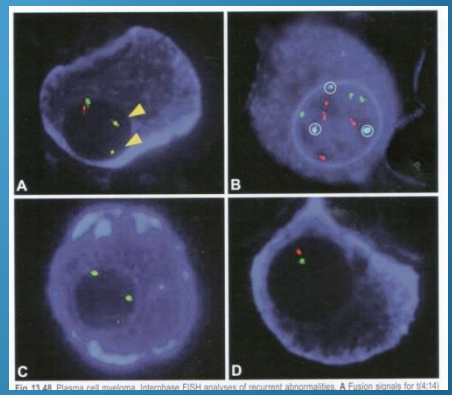
XIX CORSO DI AGGIORNAMENTO PER OPERATORI DEI REGISTRI TUMORI

MIELOMA

QUANDO E COME REGISTRARE UN CASO





BARI 6-8 Novembre 2019

DEFINIZIONE

Il Mieloma è una neoplasia caratterizzata dalla proliferazione di un clone di plasmacellule neoplastiche che si accumulano a livello midollare e producono immunoglobuline (Ig) o frammenti di Ig tutte dello stesso tipo (componente monoclonale CM)

CATEGORIE TUMORI EMOLINFOPOIETICI

- NEOPLASIE LINFOIDI
- NEOPLASIE MIELOIDI
- **NEOPLASIE PLASMACELLULARI**
- ISTIOCITOSI

Table 13.04 Plasma cell neoplasms

Non-IgM (plasma cell) monoclonal gammopathy of undetermined significance (precursor lesion)
Plasma cell myeloma
Clinical variants:
Smouldering (asymptomatic) plasma cell myeloma
Non-secretory myeloma
Plasma cell Leukemia
Plasmacytoma
Solitary plasmacytoma of bone
Extraosseous (extramedullary) plasmacytoma
Monoclonal immunoglobulin deposition diseases
Primary amyloidosis
Systemic light and heavy chain deposition diseases
Plasma cell neoplasms with associated paraneoplastic syndrome
POEMS syndrome
TEMPI syndrome (provisional)

CITOGENESI MIELOMA

CELLULE B DEL CENTRO POST-GERMINATIVO

ETIOLOGIA

- ESPOSIZIONE ALLE RADIAZIONI IONIZZANTI
- ESPOSIZIONE A PESTICIDI
- ESPOSIZIONE A METALLI PESANTI
- FUMO DI SIGARETTA
- ALCOOL
- FAMILIARITA’

ESAMI DIAGNOSTICI

- ESAMI EMATICI
- ESAME URINE
- ASPIRATO MIDOLLARE
- BIOPSIA MIDOLLARE
- ANALISI CITOGENETICA (FISH)
- WHOLE-BODY LOW-DOSE CT; PET-CT; MRI, Rx sistemica scheletrica

QUADRO CLINICO-LABORATORISTICO-STRUMENTALE

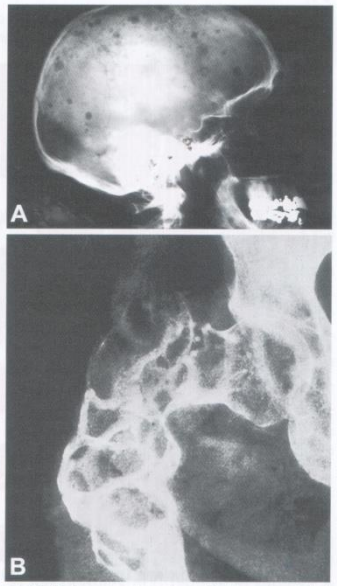
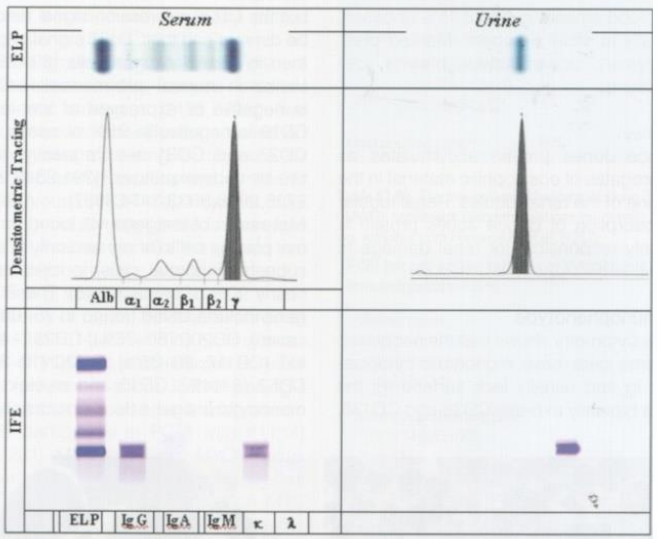


Fig. 13.38 Plasma cell myeloma. Radiographs of skull (**A**) and femoral head (**B**) demonstrate multiple lytic bone lesions.



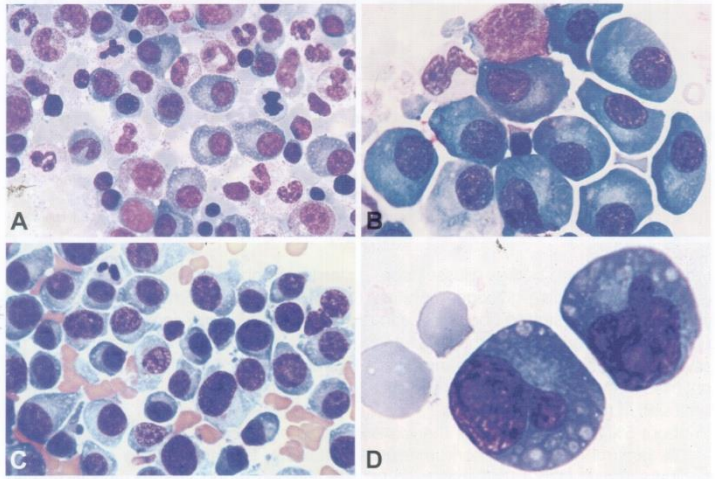


Fig. 13.45 Plasma cell myeloma. Cytological features in marrow aspirations showing variation from mature (**A**,**B**) to immature (**C**,**D**) plasma cells. The more mature cells have clumped nuclear chromatin, abundant cytoplasm, a low N:C ratio, and only rare nucleoli. In contrast, the less mature cells have more-prominent nucleoli, loose reticular chromatin, and a higher N:C ratio.

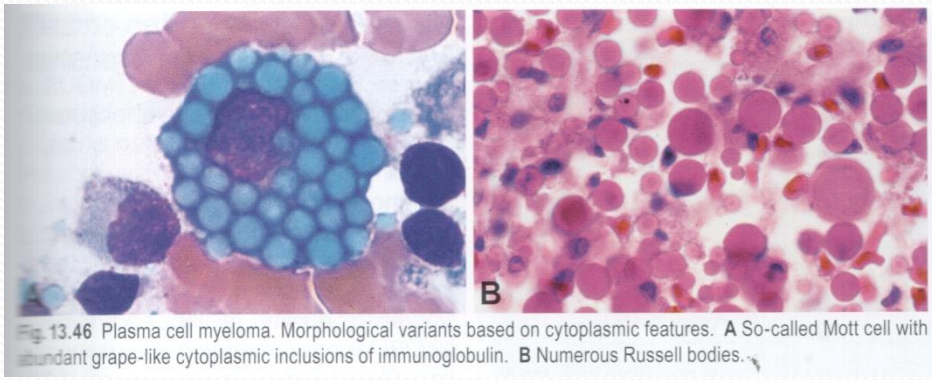
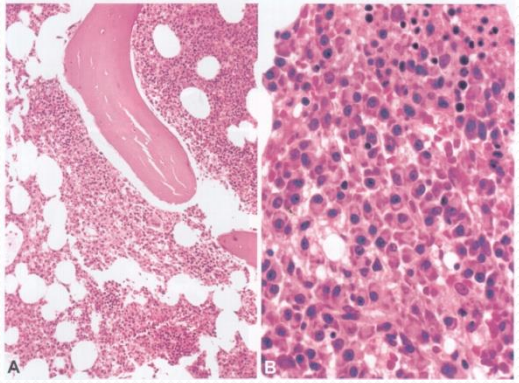
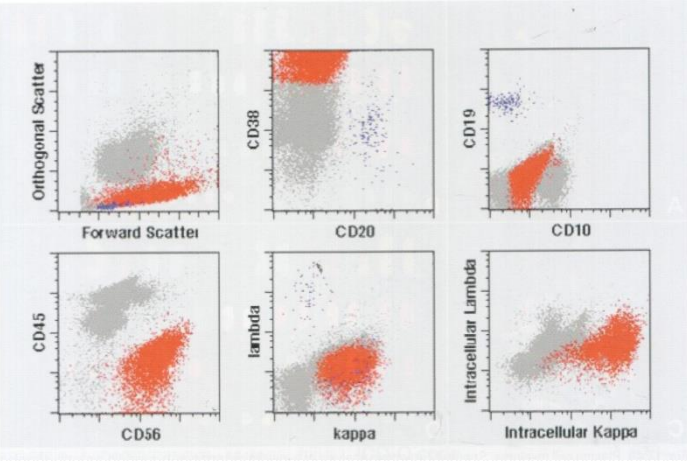


Fig. 13.46 Plasma cell myeloma. Morphological variants based on cytoplasmic features. **A** So-called Mott cell with abundant grape-like cytoplasmic inclusions of immunoglobulin. **B** Numerous Russell bodies.



QUADRO-CLINICO-LABORATORISTICO-STRUMENTALE



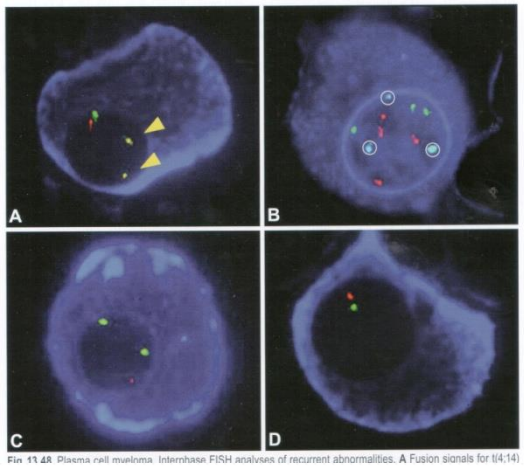


Fig. 13.48 Plasma cell myeloma. Interphase FISH analyses of recurrent abnormalities. A Fusion signals for t(4:14)

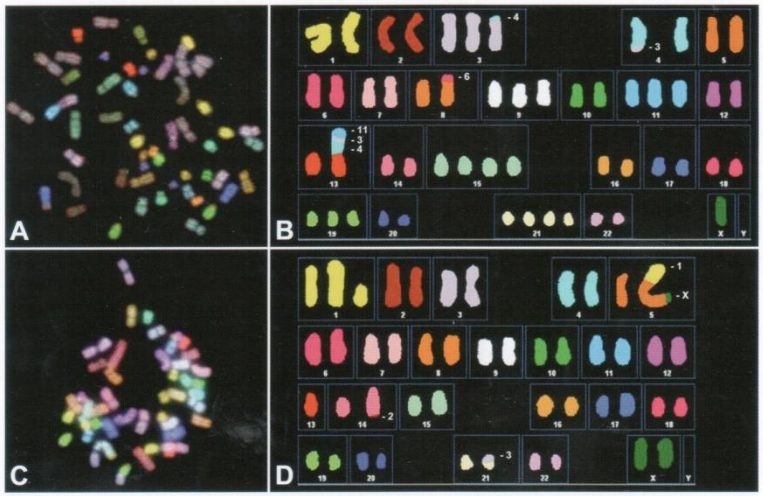


Fig. 13.49 Plasma cell myeloma. Spectral karyotypic analysis of hyperdiploid and non-hyperdiploid cases, showing

CRITERI DIAGNOSTICI

Diagnosi	Definizione
MGUS (non-IgM)	▪ Componente monoclonale (non IgM) < 3 g/dl ▪ Plasmacellule midollari monoclonali < 10% ▪ Assenza di segni/sintomi di danno d'organo correlabili alla discrasia plasmacellulare
MGUS a catene leggere (light chain)	▪ Rapporto catene leggere libere sieriche alterato (<0,26 o >1,65) con incremento relativo nella catena kappa o lambda ▪ Assenza di catena leggera pesante all'immunofissazione ▪ Proteinuria monoclonale < 500 mg/die ▪ Plasmacellule midollari monoclonali < 10% ▪ Assenza di segni/sintomi di danno d'organo correlabili alla discrasia plasmacellulare
SMM plasmacellule monoclonali midollari	▪ Componente monoclonale (IgG o IgA) ≥ 3gr/dl o proteinuria monoclonale ≥ 500 mg/die e/o 10-60% di ▪ Assenza di segni/sintomi di danno d'organo correlabili alla discrasia plasmacellulare
MM	▪ ≥10% di plasmacellule monoclonali midollari o biopsia diagnostica per plasmocitoma osseo o solitario e almeno 1 dei seguenti Myeloma Defining Events: - Ipercalcemia (calcio sierico >0,25 mmol/L/1 mg/dl rispetto al limite superiore o > 2,75 mmol/L/11 mg/dL) - Insufficienza renale: clearance della creatinina < 40 ml/min o creatinina sierica >177 µmol/l (>2 mg/dl) - Anemia: riduzione dei valori di Hb > 2 g/dl rispetto al limite inferiore normale o Hb < 10 g/dl - Lesioni ossee: 1 o più lesioni osteolitiche in radiografia convenzionale, tomografia computerizzata (TC) o tomografia ad emissione di positroni (PET)- TC - Plasmacellule monoclonali midollari ≥60% - Rapporto tra catene leggere libere sieriche (catena coinvolta / non coinvolta) > 100 - ≥1 lesione focale in RMN
Plasmocitoma solitario	▪ Plasmacellule monoclonali su lesione ossea solitaria o tessuto molle ▪ Assenza di plasmacellule monoclonali su midollo emopoietico ▪ Assenza di lesioni radiologiche (eccetto la lesione solitaria primitiva) ▪ Assenza di segni/sintomi di danno d'organo correlabili alla discrasia plasmacellulare
Plasmocitoma solitario con minima invasione midollare	▪ Plasmacellule monoclonali su lesione ossea solitaria o tessuto molle ▪ Plasmacellule monoclonali midollari <10% ▪ Assenza di lesioni radiologiche (eccetto la lesione solitaria primitiva) ▪ Assenza di segni/sintomi di danno d'organo correlabili alla discrasia plasmacellulare

Criteri diagnostici per MGUS, SMM, MM e Plasmocitoma

Plasmacellule monoclonali midollare >10% o plasmocitoma extramidollare e almeno 1 dei seguenti segni/sintomi di malattia:

- Ipercalcemia (calcio sierico ≥ 11 mg/dl o >1 mg/dl rispetto al limite superiore).
- Insufficienza renale (clearance della creatinina < 40 ml/min o creatinina sierica ≥ 2mg/dl)
- Anemia (Hb > 2g/dl al limite inferiore di norma o Hb < 10 g/dl)
- Lesioni osteolitiche: 1 o più lesioni osteolitiche evidenziate mediante Rx, Tc o PET/TC
- Plasmacellule monoclonali ≥ 60%
- K/L libere sieriche >100
- ≥1 lesione focali evidenziata mediante RMN

Criteri per la diagnosi di MM sintomatico

STADIAZIONE

Table 4: Staging Systems for Multiple Myeloma

Stage	Durie-Salmon Criteria	International Staging System (ISS)
I	All of the following: • Hemoglobin value > 10 g/dL • Serum calcium value normal or ≤ 12 mg/dL • Bone X-ray shows normal bone structure or solitary bone plasmacytoma only • Low M-component production rate: IgG value < 5g/dL IgA value < 3 g/dL Bence Jones protein < 4 g/24 h	Serum beta-2 microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL
II	Neither stage I nor stage III	Neither stage I nor stage III
III	One or more of the following: • Hemoglobin value < 8.5 g/dL • Serum calcium value > 12 mg/dL • Advanced lytic bone lesions • High M-component production rate[a] IgG value > 7 g/dL IgA value > 5 g/dL Bence Jones protein > 12 g/24 h	Serum beta-2 microglobulin ≥ 5.5 mg/L
Subclassification Criteria A = Normal renal function (serum creatinine level < 2.0 mg/dL) B = Abnormal renal function (serum creatinine level ≥ 2.0 mg/dL)		

[a]M-component refers to the abnormal monoclonal protein that in most patients is secreted by the myeloma cells.

Information from References 8,12, and 44.

CRITERI PROGNOSTICI

Table 13.11 International Staging System (ISS) for plasma cell myeloma. From Greipp PR, et al. {1456}

Stage	Criteria	Median survival (months)
I	Serum beta-2 microglobulin < 3.5 g/dL Serum albumin ≥ 3.5 g/dL	62
II	Not stage I or III[a]	44
III	Serum beta-2 microglobulin ≥ 5.5 mg/L	29

[a] There are two categories for stage II:
(1) serum beta-2 microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL and
(2) serum beta-2 microglobulin of 3.5 to < 5.5 mg/L, irrespective of the serum albumin level.

Table 13.12 Mayo Stratification of Myeloma and Risk-Adapted Therapy. Adapted from Chesi M and Bergsagel PL {69

Standard risk (60%)	Intermediate risk (20%)	High risk (20%)
t(11;14)	t(4;14)	Del 17p
t(6;14)	Del 13	t(14;16)
Hyperdiploid	Hypodiploid	t(14;20)
All others		GEP high-risk signature
OS: 8–10 years	OS: 4–5 years	OS: 3 years

GEP, gene expression profiling; OS, overall survival.

Table 13.10 Molecular classifications of plasma cell myeloma[a]; modified from Kuehl WM and Bergsagel PL {2128}

Group	TC[b]	Gene[c]	Ploidy	%[d]	UAMS	HOVON-GMMG
Cyclin D TLC	11q13	*CCND1*	N	15	CD1, CD2	CD1, CD2
	6p21	*CCND3*	N	2	CD1, CD2	CD1, CD2
	12p13	*CCND2*	N	<1	CD1, CD2	CD1, CD2
NSD2[e] TLC	4p16	*NSD2, FGFR3 (CCND2)*	N > H	15	MS	MS
MAF TLC	16q23	*MAF (CCND2)*	N	5	MF	MF
	20q12	*MAFB (CCND2)*	N	2	MF	MF
	8q24	*MAFA (CCND2)*	N	<1	MF	MF
No primary TLC	D1	*CCND1*	H	33	HY	Y, CD1, NFKB, CTA, PRL3
	D1 + D2	*CCND1, CCND2*	H	7	PR	PR, CTA
	D2	*CCND2*	H, NH	18	PR, LB	LB, CTA, PRL3
	None[f]	No cyclin D genes	N	2	PR	PR, CTA

H, mostly hyperdiploid; HOVON-GMMG, Dutch-Belgian Cooperative Trial Group for Hematology-Oncology and German Multiple Myeloma Group classification; N, mostly non-hyperdiploid; PR, proliferation; TC, translocations and cyclin D classification; TLC, IGH translocation; UAMS, University of Arkansas for Medical Science classification.

[a] The TC classification is generally valid for monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma. The UAMS and HOVON-GMMG classifications include plasma cell myeloma progression events and are probably not generally valid for MGUS.
[b] 11q13 and 6p21 are combined into one TC group; 12p13 is rarely identified and thus usually in the D2 group.
[c] TLC target and/or cyclin D upregulated
[d] The percentage of patients with plasma cell myeloma in each group. [e]*NSD2* is also known as *MMSET*.
[f] None refers to a group of patients with no cyclin D expression.

Table 13.08 The International Myeloma Working Group (IMWG) molecular cytogenetic classification of plasma cell myeloma. Adapted from Fonseca R, et al. {1232}

Genetic category	Proportion of cases
Hyperdiploid	45%
Non-hyperdiploid	40%
Cyclin D translocation	18%
t(11;14)(q13;q32)	16%
t(6;14)(p25;q32)	2%
t(12;14)(p13;q32)	<1%
NSD2 (also called *MMSET*) translocation	15%
t(4;14)(p16;q32)	15%
MAF translocation	8%
t(14;16)(q32;q23)	5%
t(14;20)(q32;q11)	2%
t(8;14)(q24;q32)	1%
Unclassified (other)	15%

Table 13.09 The International Myeloma Working Group (IMWG) consensus recommendations on genetic testing. Adapted from Fonseca R, et al. {1232}

FISH (on cell-sorted samples or cytoplasmic immunoglobulin FISH)

Minimal panel:
t(4;14)(p16;q32),
t(14;16)(q32;q23),
del(17p13.1)

More comprehensive panel:
t(11;14)(q13;q32),
del 13,
ploidy category,
chromosome 1 abnormalities

Clinical trials should incorporate gene expression profiling

STADIAZIONE

Table 4: Staging Systems for Multiple Myeloma

Stage	Durie-Salmon Criteria	International Staging System (ISS)
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II	Neither stage I nor stage III	Neither stage I nor stage III
III	One or more of the following: • Hemoglobin value < 8.5 g/dL • Serum calcium value > 12 mg/dL • Advanced lytic bone lesions • High M-component production rate[a] IgG value > 7 g/dL IgA value > 5 g/dL Bence Jones protein > 12 g/24 h	Serum beta-2 microglobulin ≥ 5.5 mg/L
Subclassification Criteria A = Normal renal function (serum creatinine level < 2.0 mg/dL) B = Abnormal renal function (serum creatinine level ≥ 2.0 mg/dL)		

[a]M-component refers to the abnormal monoclonal protein that in most patients is secreted by the myeloma cells.

Information from References 8,12, and 44.

CLASSIFICAZIONE WHO 2017

- 9765/1 Non IgM MGUS
- 9732/3 Mieloma Plasmacellulare
- 9732/3 Mieloma Smouldering
- 9732/3 Mieloma, NAS
- 9731/3 Plasmocitoma solitario dell'osso
- 9734/3 Plasmocitoma extraosseo

CODIFICA

- **CODICE TOPOGRAFICO**
- C42.0 SANGUE
- **C42.1 MIDOLLO OSSEO**
- C42.2 MILZA
- C42.3 SISTEMA RETICOLOENDOTELIALE,NAS
- C42.4 SISTEMA EMOPOIETICO,NAS
- **CODICE MORFOLOGICO ICDO 3**
- **9731-9734**
- **GRADING/DIFFERENZIAZIONE/IMMUNOFENOTIPO**
- CODICI (1; 2; 3; 4; 5; 6; 7; 8; 9)
- **BASE DIAGNOSI** CODICI (0; 1 ; 2; 3; 4; **5,7**; 6)
- **DATA DIAGNOSI** DATA DI PRIMA DIAGNOSI

CODIFICA

- **GRADING/DIFFERENZIAZIONE/IMMUNOFENOTIPO**
- CODICI (1; 2; 3; 4; 5; 6; 7; 8; 9)
- 1 Grado 1 Ben differenziato Differenziato, NAS
- 2 Grado 2 Moderatamente differenziato
- 3 Grado 3 Scarsamente differenziato
- 4 Grado 4 Indifferenziato; Anaplastico
- 5 Cellule T
- **6 Cellule B; Pre-B; Precursori B**
- 7 Cellule null; Non T-Non B
- 8 Cellule N-K; Cellule Natural-Killer
- 9 Grado o differenziazione indeterminata, non definito o non applicabile

BASE DIAGNOSI (1)

- **0 DCO**
- **1 CLINICA**
- Esenzione ticket
- MMG
- Anamnesi/Invalidità
- SDO
- **2 STRUMENTALE**
- Radiografia
- Ecografia
- TAC
- RMN
- Scintigrafia
- Chemioterapia/Radioterapia
- Termo/crioablazione
- Endoscopia
- **5 CITOLOGICA**
- Urine
- Espettorato
- Versamento
- Brushing/Lavaggio
- Agoaspirato FNA
- PAP test
- **Striscio sangue periferico**
- **Aspirato midollare**
- **Citogenetica/Biologia molecolare**

BASE DIAGNOSI (2)

- **6 ISTOLOGIA SU METASTASI**
- Istologia su linfonodo regionale
- Istologia su metastasi a distanza
- **7 ISTOLOGIA SU TUMORE PRIMITIVO**
- Istologia su biopsia
- Istologia su TUR
- Istologia su cono
- **BOM**
- Istologia su pezzo
- **8 ISTOLOGIA SU AUTOPSIA**
- Riscontro incidentale
- Riscontro non incidentale
- **9 NON NOTO**

DATA DI INCIDENZA O DI DIAGNOSI

- Data della prima conferma cito-istologica
- Usare la data di esecuzione del prelievo o in mancanza la data di accettazione, non usare mai la data di refertazione
- Data del ricovero in cui viene posta diagnosi di tumore
- Retrodatare la data di incidenza rispetto alla data di ricovero in presenza di indicazioni anamnestiche remote o di indicazioni del tempo di insorgenza nei certificati di decesso
- Data di altra diagnosi clinica/strumentale di tumore per i pazienti non ricoverati
- Data del decesso