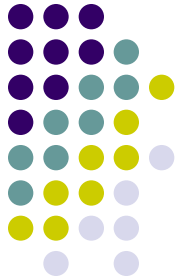
CARENZA ED ECCESSO DI FERRO

NUOVE CONOSCENZE ED APPROCCIO TERAPEUTICO



ESPERIENZE DELLA CHELAZIONE NELLE EMOGLOBINOPATIE DELL'ADULTO

M Rita Gamberini

DH della Talassemia e delle Emoglobinopatie

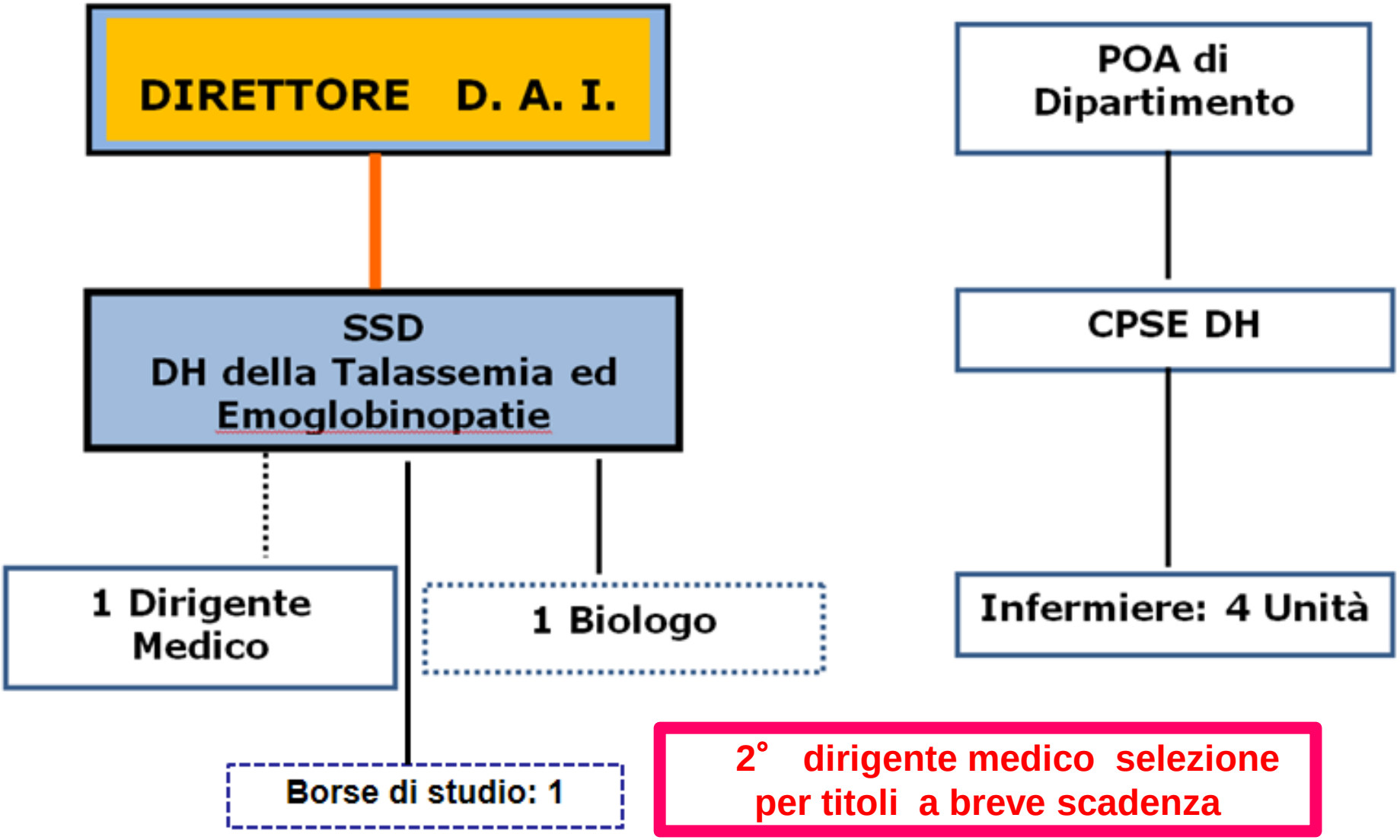
Dipartimento Accrescimento e Riproduzione

Azienda Universitario-Ospedaliera

Cona-Ferrara

18 NOVEMBRE 2016

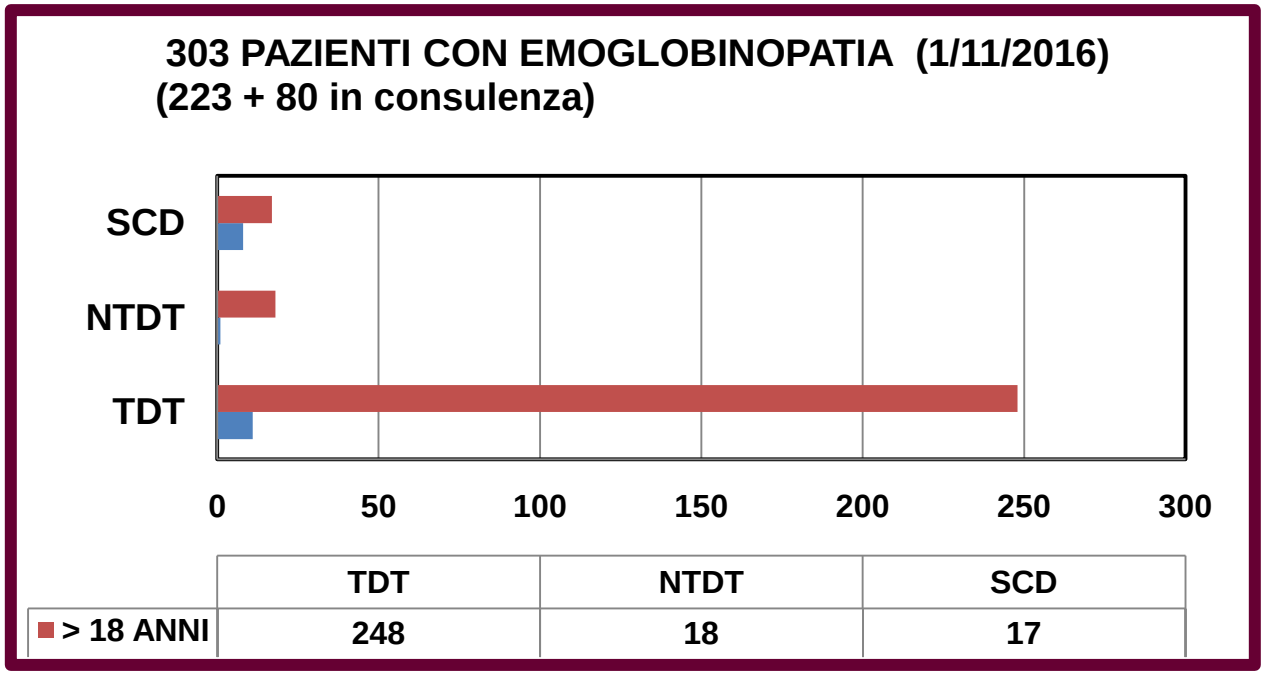
ORGANIGAMMA DHTE

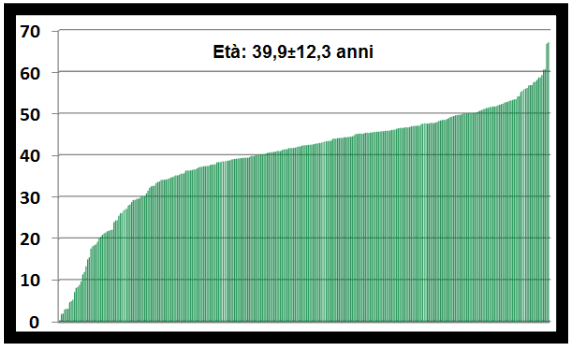


Attività assistenziale 2016

- **Talassemia major: 173**
- **Talassemia intermedia TD : 15**
- **Talassemia intermedia NTD: 18**
- **Sindrome drepanocitica: 17 (7 E-Ex; 2 trasfus semp)**

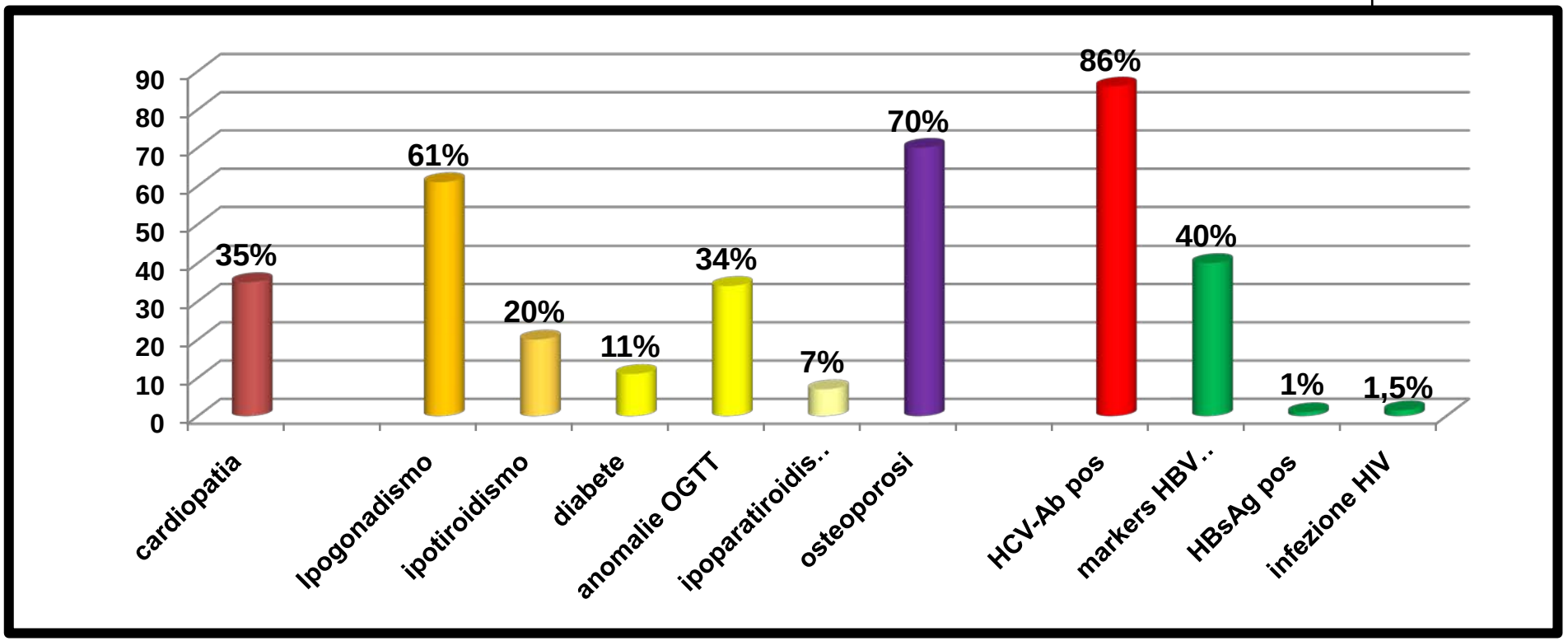
- **In consulenza da altri centri: 80**

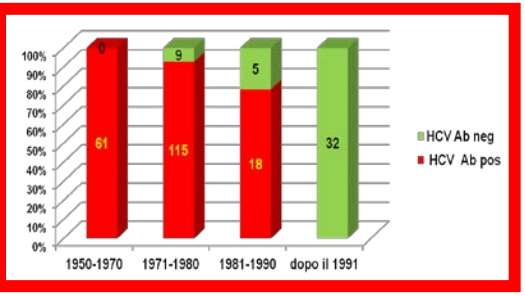


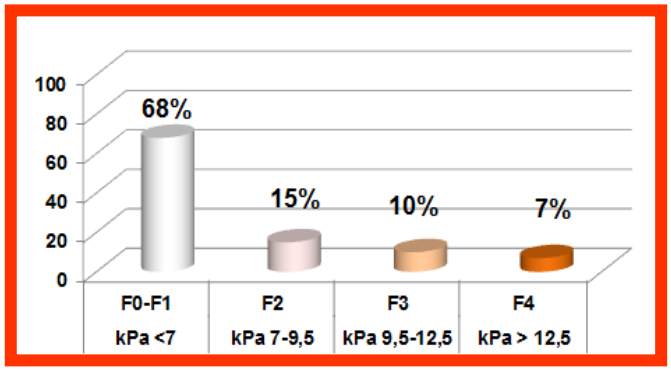


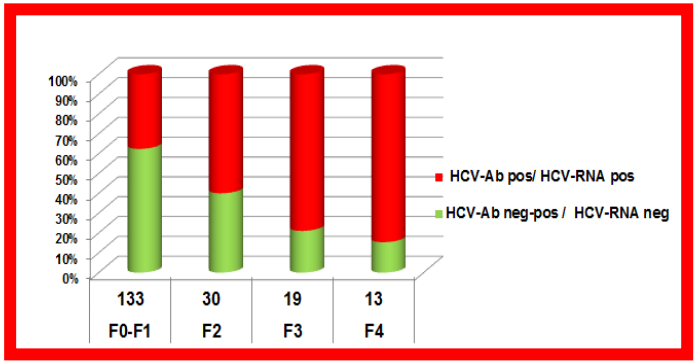
Complicanze in pazienti adulti con TD talassemia

Numero di pazienti	195
Età (anni)	38,6 ± 6,9 (18-54)
Sesso	F: 109; M:86
Diagnosi	TM:176; TITD: 19

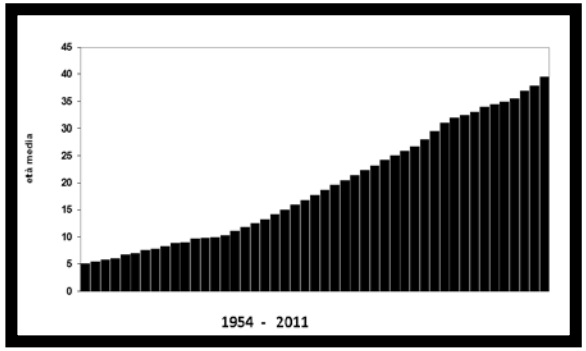


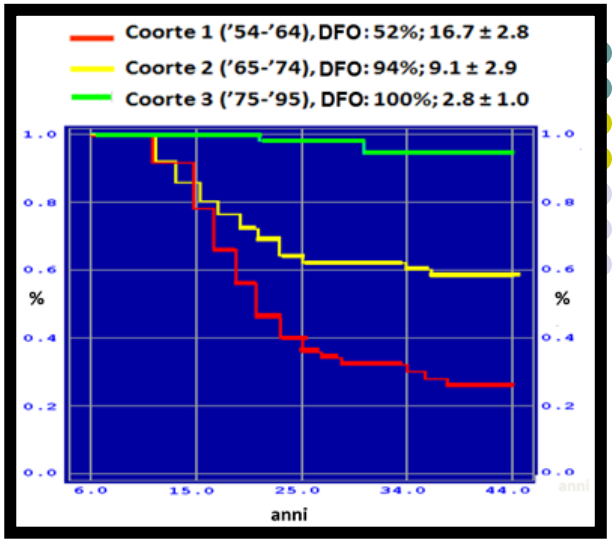


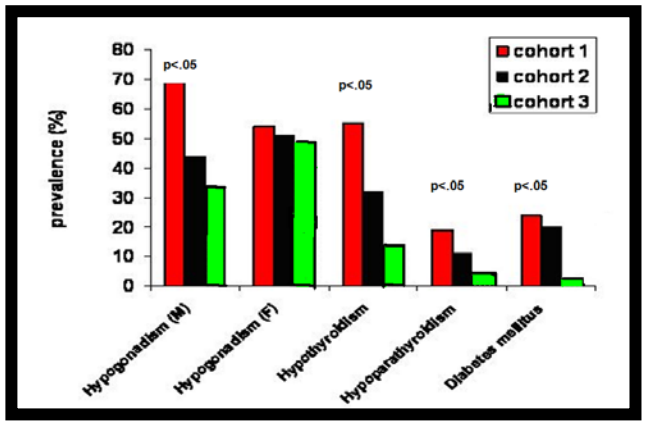


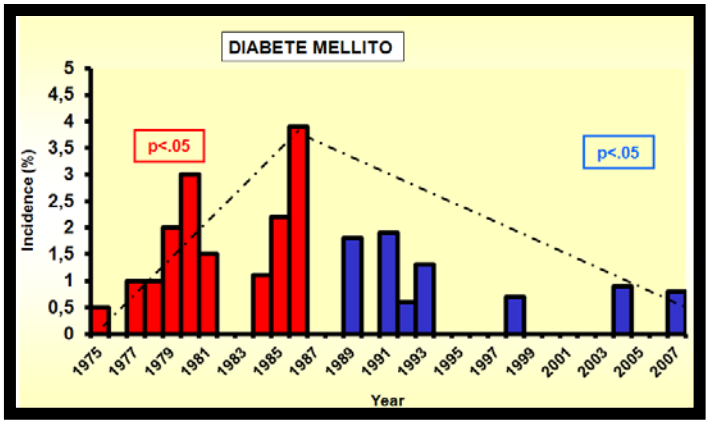


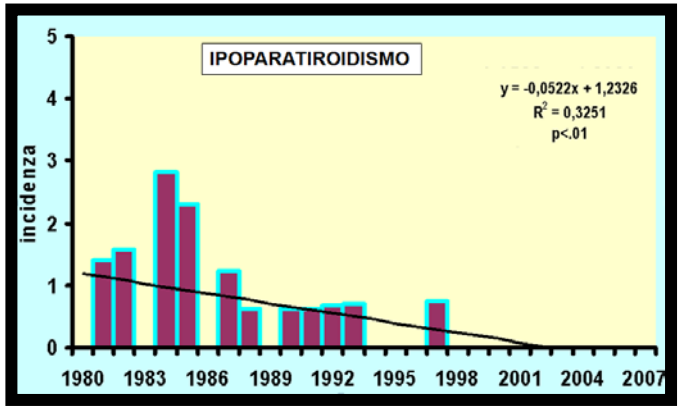
TDT: sopravvivenza e complicanze endocrine

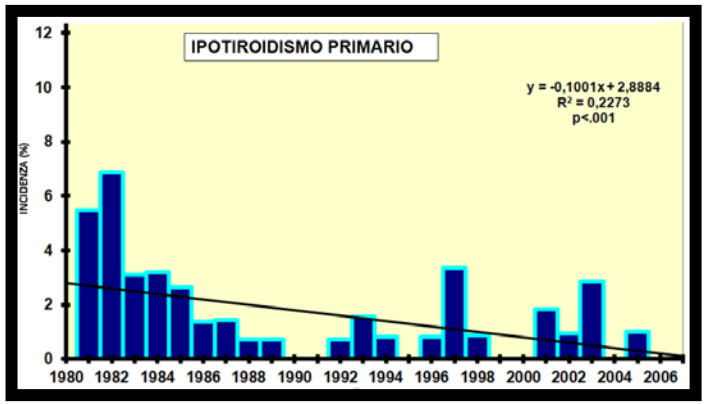












LA TERAPIA CHELANTE (TDT)

Farmaci chelanti:

- **monoterapia**
  - **Desferioxamina (sc): dal 1979**
  - **Deferiprone (orale): dal 1995**
  - **Deferasirox (orale): dal 2004**
- **associata:**
  - **DFO+DPO combinata: dal 2002**

Obiettivi della terapia chelante:

- **Ferritina : < 1000 ng/ml**
- **LIC: 3-7 mg/ g tes**
- **T2* cardiaco: > 20 ms**

Diagnostica per valutare il sovraccarico di ferro:

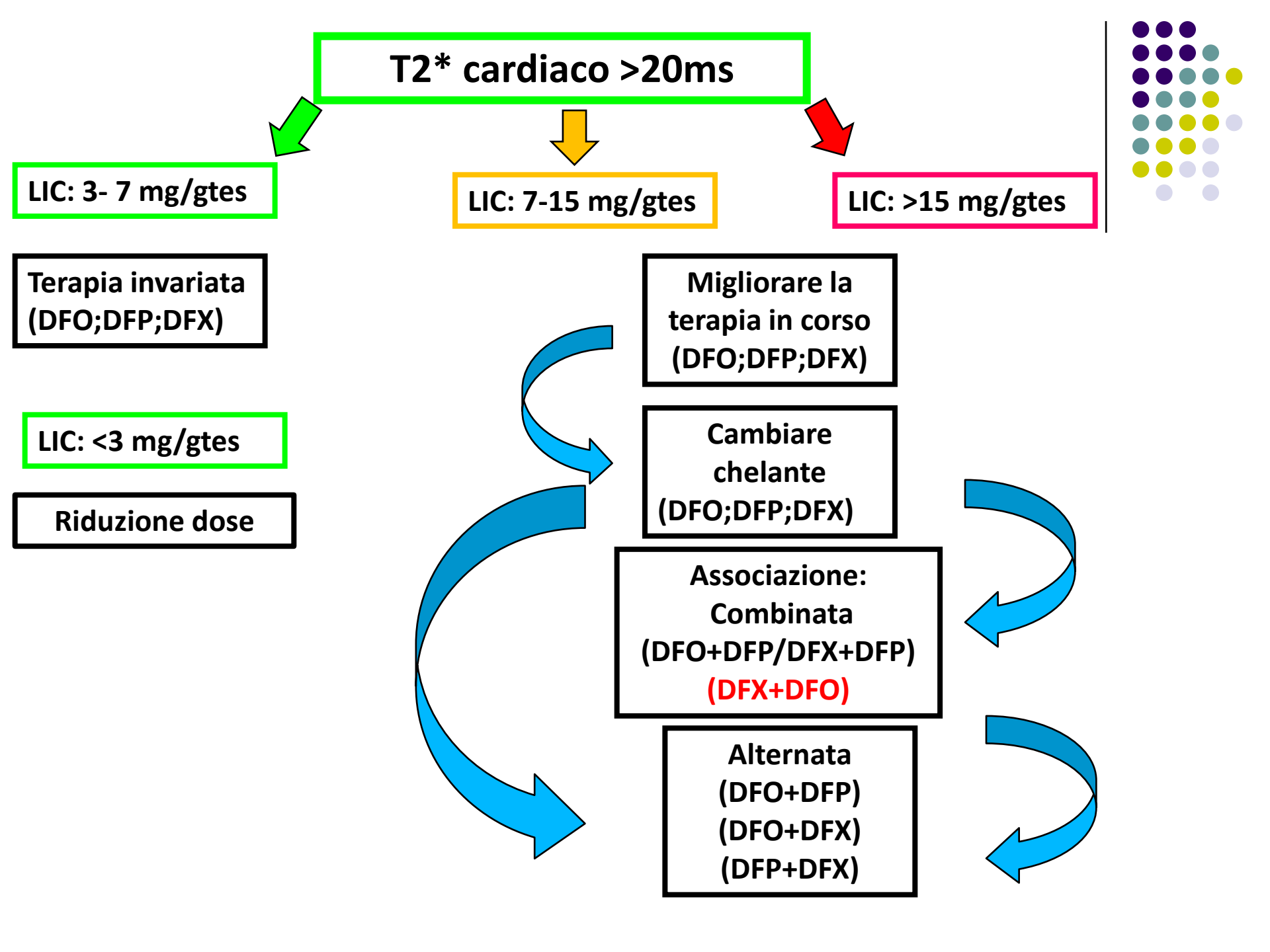
- **1979**: ***dosaggio della ferritina sierica***
- **Anni '80**: **biopsia epatica**
- **Anni ' 90 : SQUID (Amburgo, Torino)**
- **2004**: **RM fegato-cuore**
  studio MIOT (2009)

Valutazione periodica dei depositi di ferro

Ferritina: 1-3 mesi

RM fegato-cuore:

- 12-18 mesi
- prima di un cambiamento drastico della terapia chelante
- 6 mesi depositi elevati
- Incremento (> 1500) o riduzione (< 500) della ferritina


T2* cardiaco >20ms
LIC: 3- 7 mg/gtes
LIC: 7-15 mg/gtes
LIC: >15 mg/gtes
Terapia invariata (DFO;DFP;DFX)
Migliorare la terapia in corso (DFO;DFP;DFX)
LIC: <3 mg/gtes
Cambiare chelante (DFO;DFP;DFX)
Riduzione dose
Associazione: Combinata (DFO+DFP/DFX+DFP) (DFX+DFO)
Alternata (DFO+DFP) (DFO+DFX) (DFP+DFX)

2014

T2* cardiaco <20ms

T2*C: 10-20 ms

LIC: 3-15 mg/gtes

- **Terapia combinata**
  DFO sc 40-60mg/kg 3-6/7
  +
  DFP 75-100mg/kg 7/7

LIC: >15 mg/gtes

- **Terapia combinata**
  DFO sc 40-60mg/kg 6-7/7
  +
  DFP 75-100mg/kg 7/7

T2*C: <10 ms
FEV sn >56%

- **Terapia combinata**
  DFO sc 40-60mg/kg 5-7/7
  +
  DFP 75-100mg/kg 7/7

T2*C: <10 ms
FEV sn <56%
scompenso cardiaco

- **Terapia combinata**
  DFO sc ev 24 h
  40-60mg/kg 7/7
  +
  DFP 75- 100mg/kg 7/7

Miglioramento clinico

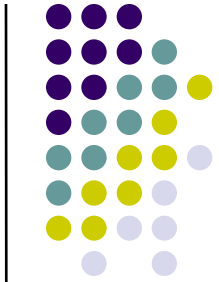
- **Terapia combinata**
  DFO sc
  40-60mg/kg 7/7 12-24 h
  +
  DFP 75-100mg/kg 7/7

In alternativa:

- **DFX: 30-40 mg/kg**
- **DFO : 40-60 mg/kg 7/7**
- **DFP: 75-100 mg/kg**

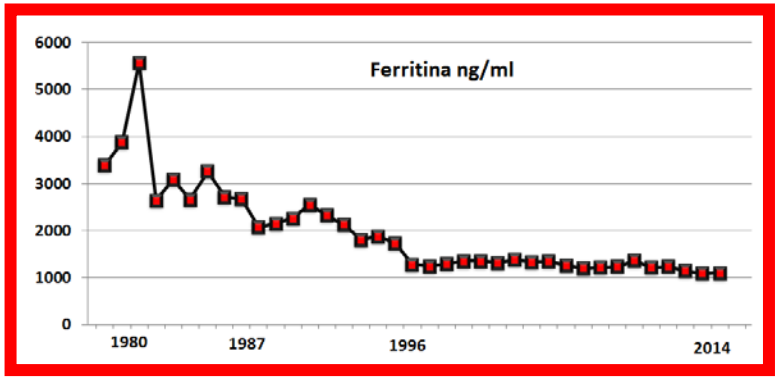
Altra terapia di associazione

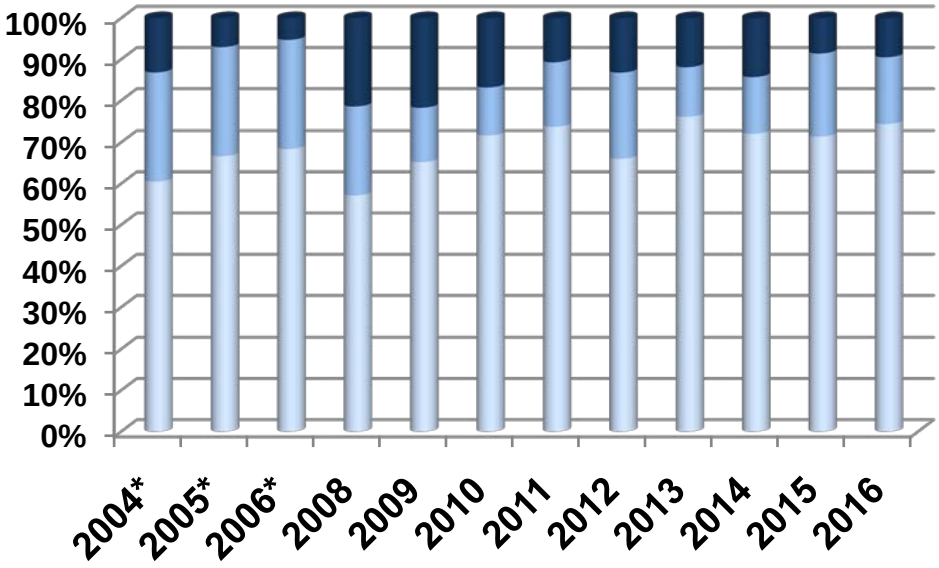
Individualizzare la terapia chelante



- **Età**
- **Depositi di ferro attuali e pregressi**
- **Ingresso di ferro trasfusionale**
- **Complicanze da ferro (cardiache, endocrine, epatiche)**
- **Terapie precedenti: efficacia,effetti tossici**
- **Situazione infettivologica**
- **Altra terapia in atto (antivirali, Hyd)**
- **Trapianto, gravidanza,terapia antivirale HCV**
- **Gravidanza in atto, allattamento**
- **Qualità di vita**
- **Adesione alla terapia**

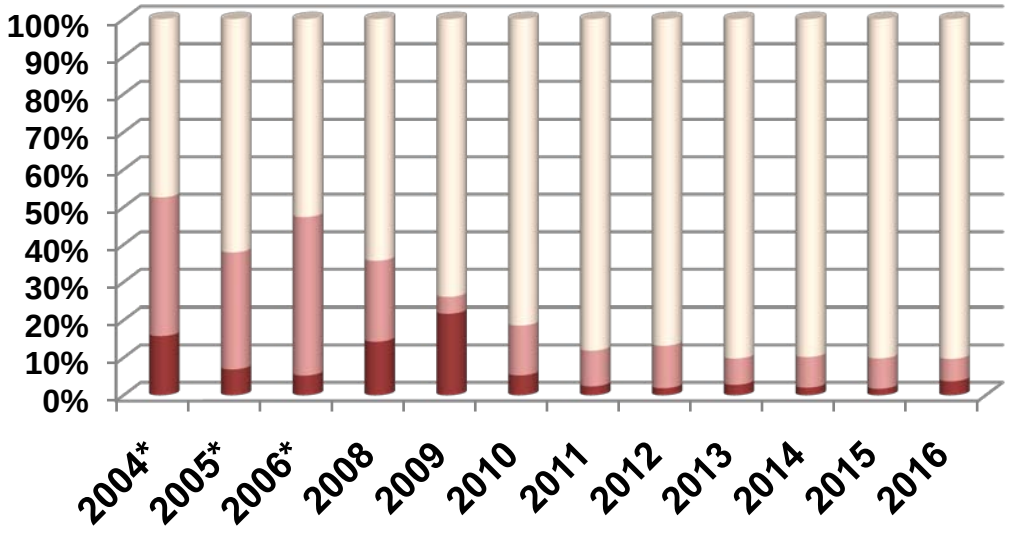
Depositi di ferro (TDT)





- > 15 mg/g tes
- 7-15 mg/g tes
- <7 mg/g tes

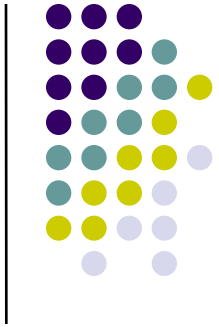
LIC



T2*C

- >20 ms
- 10-20 ms
- <10 ms

Terapia chelante attuale in TDT (1/11/2016)

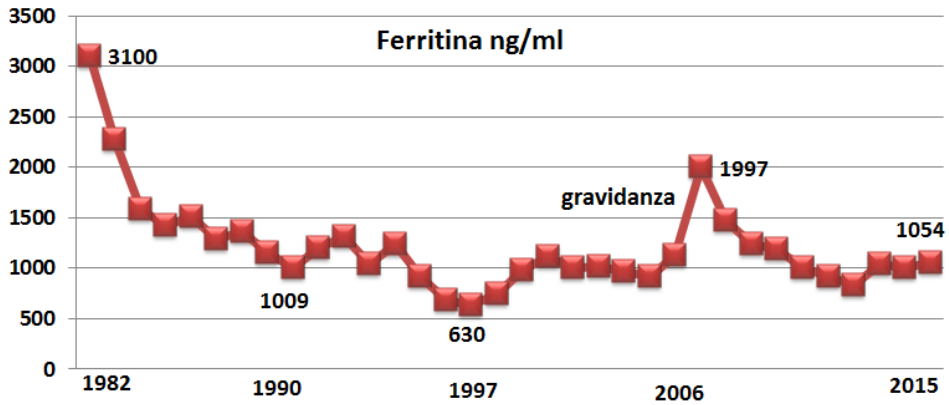


MONOTERAPIA		
DEFERIPRONE (DFP)	**56**	**24,2%**
DEFERASIROX (DFX)	**65**	**28,1%**
DESFERIOXMINA (DFO)	**77**	**33,3%**
ASSOCIAZIONE COMBINATA		
DFO+DFP	**30**	**12,9%**
DFO+DFX	**2**	**0,8%**
ASSOCIAZIONE ALTERNATA		
DFX+ DFO	**1**	**0,4%**
	231	

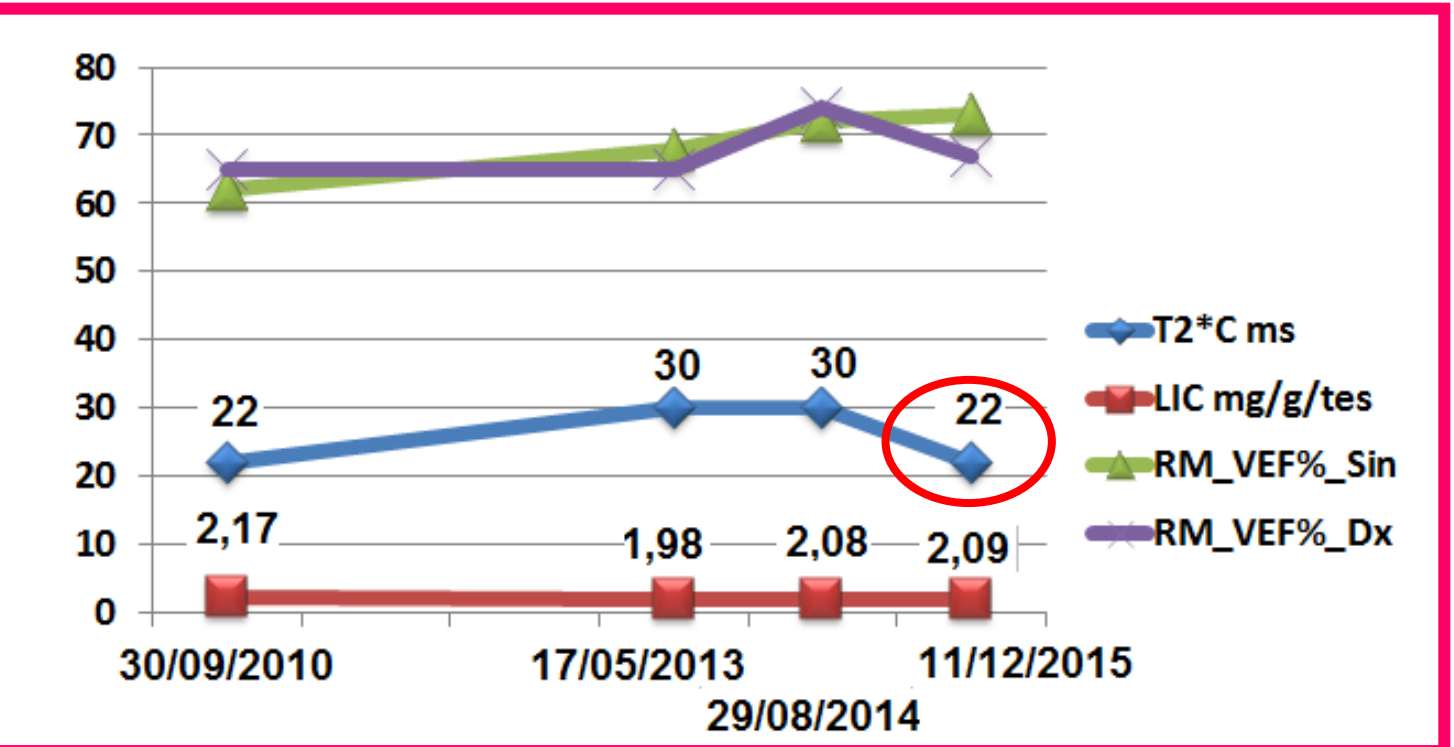
PAZIENTI IN MONOTERAPIA CON DFO

MAI USATO UN CHELANTE ORALE	34	44,2%
ALLATTAMENTO	2	2,6%
ESPERIENZA NEGATIVA CON ALMENO UNO DEI 2 CHELANTI ORALI	41	53,2%
	77	100%

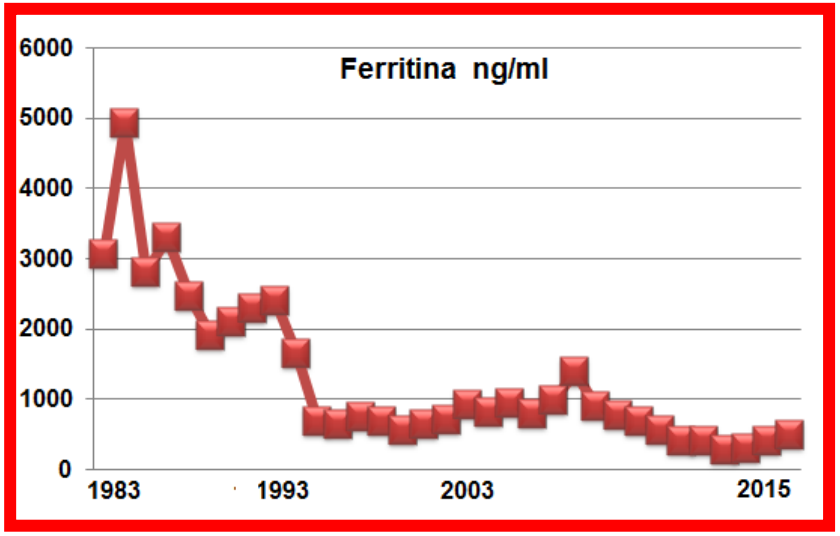
caso 1: DFO



- TM; F, 47 anni (FM, 1969)
- DFO 2 gr, 40 mg/kg, 6/7
- Iron intake: 0,38 mg/kg/die
- Litiasi colecistica
- Amenorrea primaria
- Ipotiroidismo (emitoir dx) 2011
- OGTT normale (2014)
- Protesi anca dx (artrosi) (2001)
- TIA: 2 episodi 2000
- Gravidanza indotta 2006

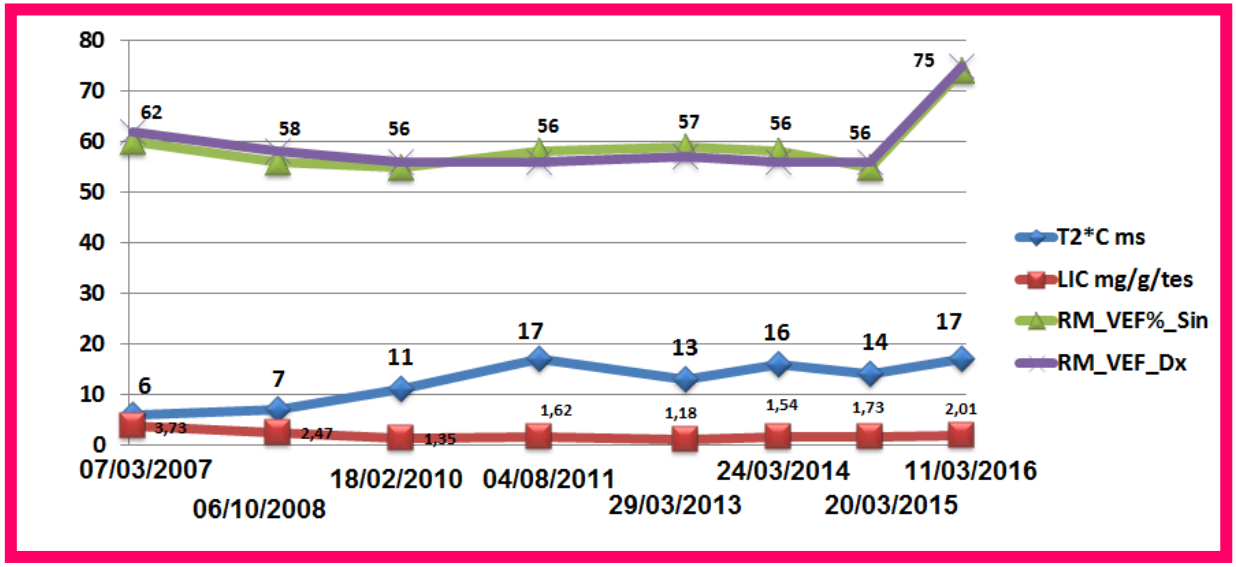


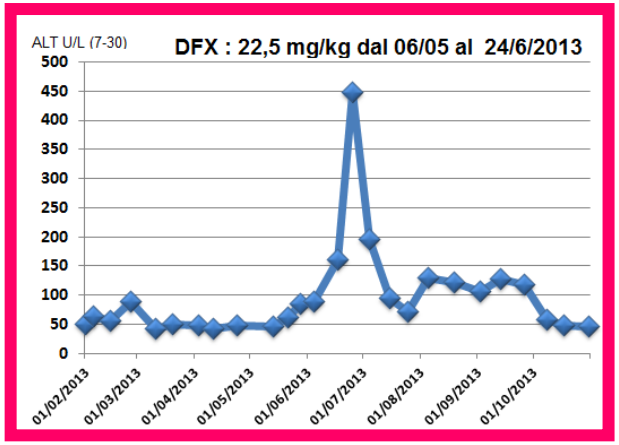
Caso 2: DFO



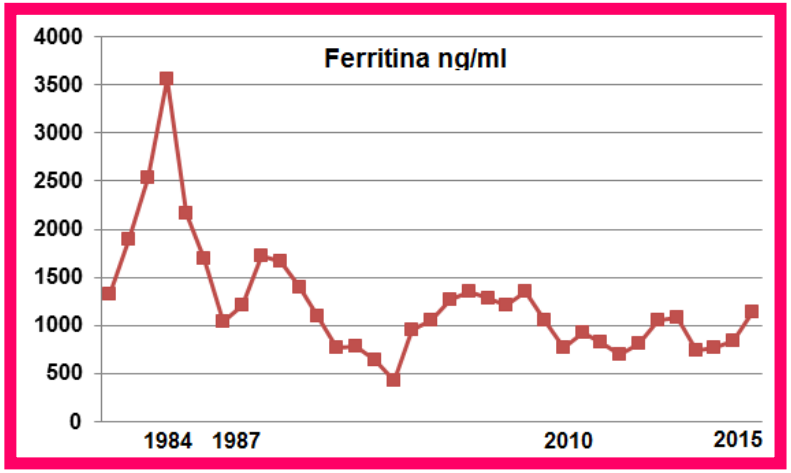
TM; F, 45 anni (BL, 1971)

- **DFO 50 mg/kg 6-7/7**
- **Iron intake: 0,4 mg/kg die**
- **Amenorrea primaria**
- **Ipoparatiroidismo (1985)**
- **Ipotiroidismo primario (1992)**
- **Osteoporosi**
- **Aritmia extrasistolica ventricolare**
- **Neutropenia ricorrente**
- **Epatite cronica HCV G1b**
- **OGTT normale (5/3/2015)**

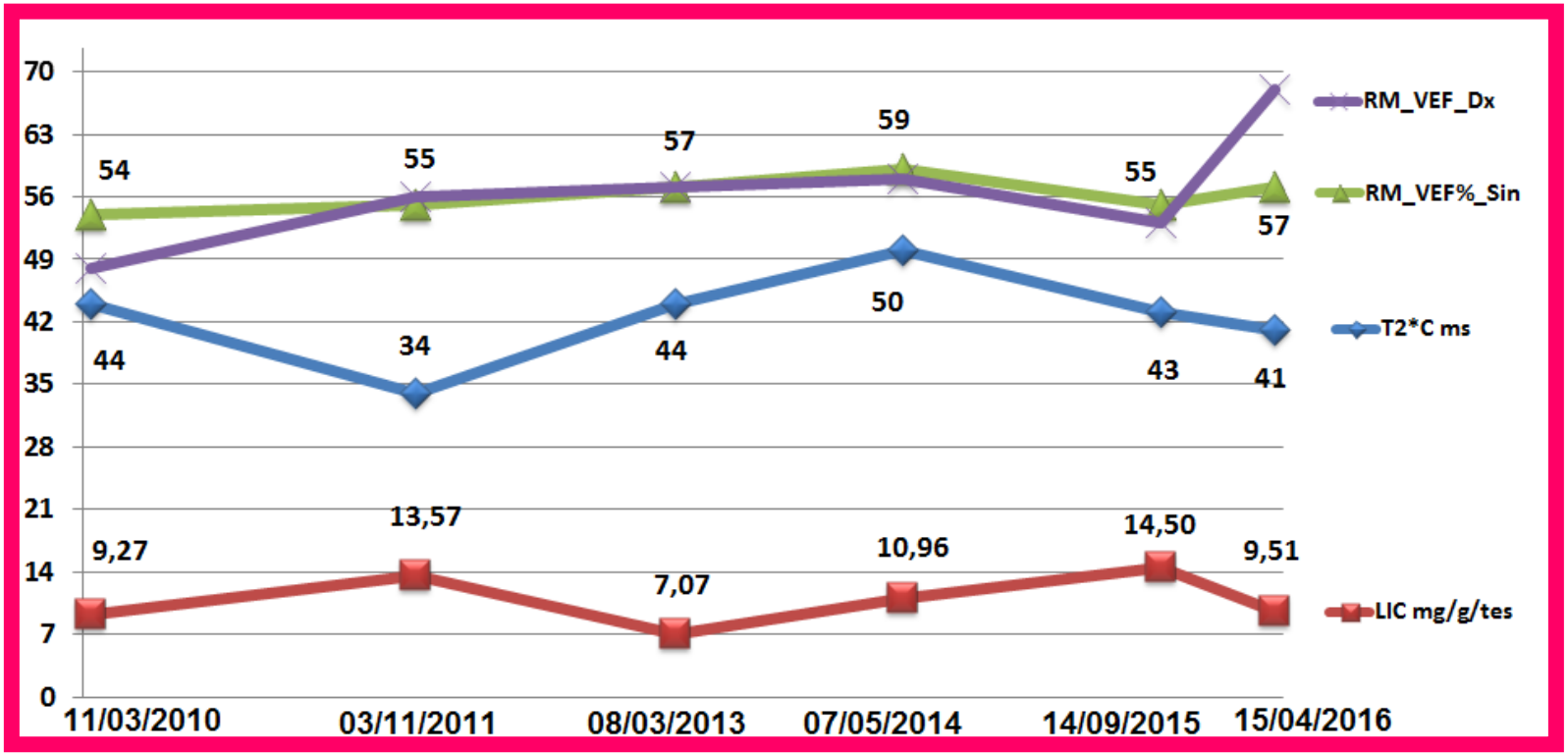




caso 3 DFO



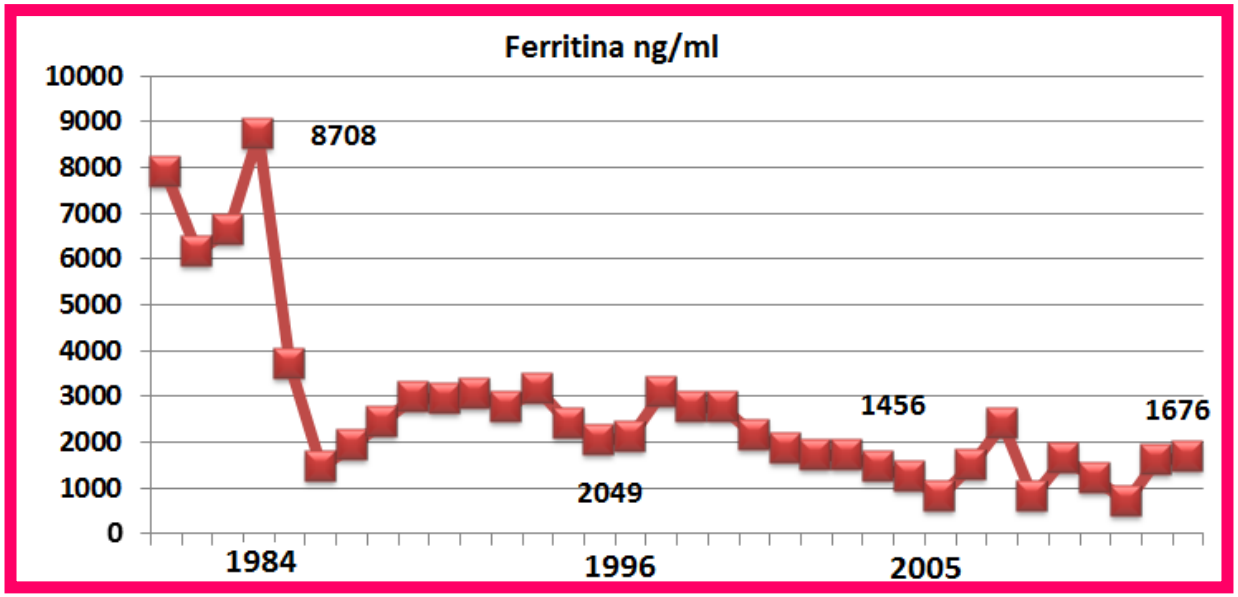
- TM; M, 42 anni (MG,1975)
- DFO: 40 mg/kg 5-6/7
- Iron intake: 0,35 mg/kg die
- Ipogonadismo puberale
- Pregressa EC – HCV (INF; 1992)
- Osteoporosi
- Litiasi colecistica (2013)
- 2010: DFX 21mg/kg; dopo 10 giorni esantema trattato con antistaminico; recidiva lieve ad un secondo tentativo



Caso 4a : paziente difficile da trattare

TM; F, 45 anni, (FS,1979)
Splenctomia (1980)

- **Ipogonadismo puberale**
- **Ipoparatiroidismo (1984)**
- **Scompenso cardiaco (1984)**
- **Ipotiroidismo primario (1983)**
- **Diabete ID (1986)**
- **Epatite cronica HCV-G1b fino al 2011 (Kpa 4,5 7/2014)**



Caso 4b : paziente difficile da trattare

Terapia chelante

DFO:

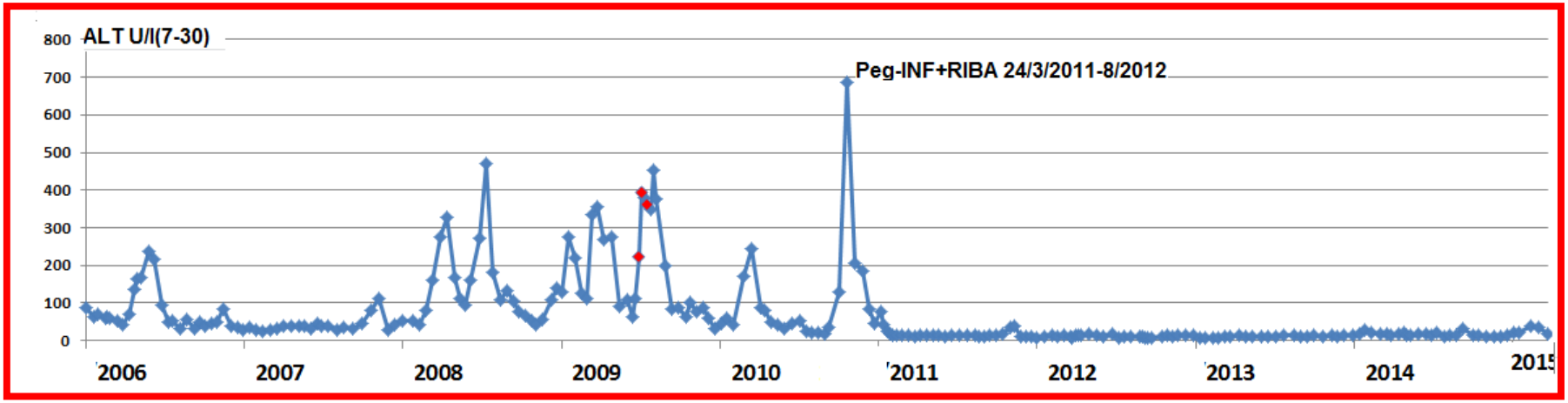
- **Reazioni locali (da sempre)**
- **Reazioni sistemiche (febbre) a periodi**

DFP:

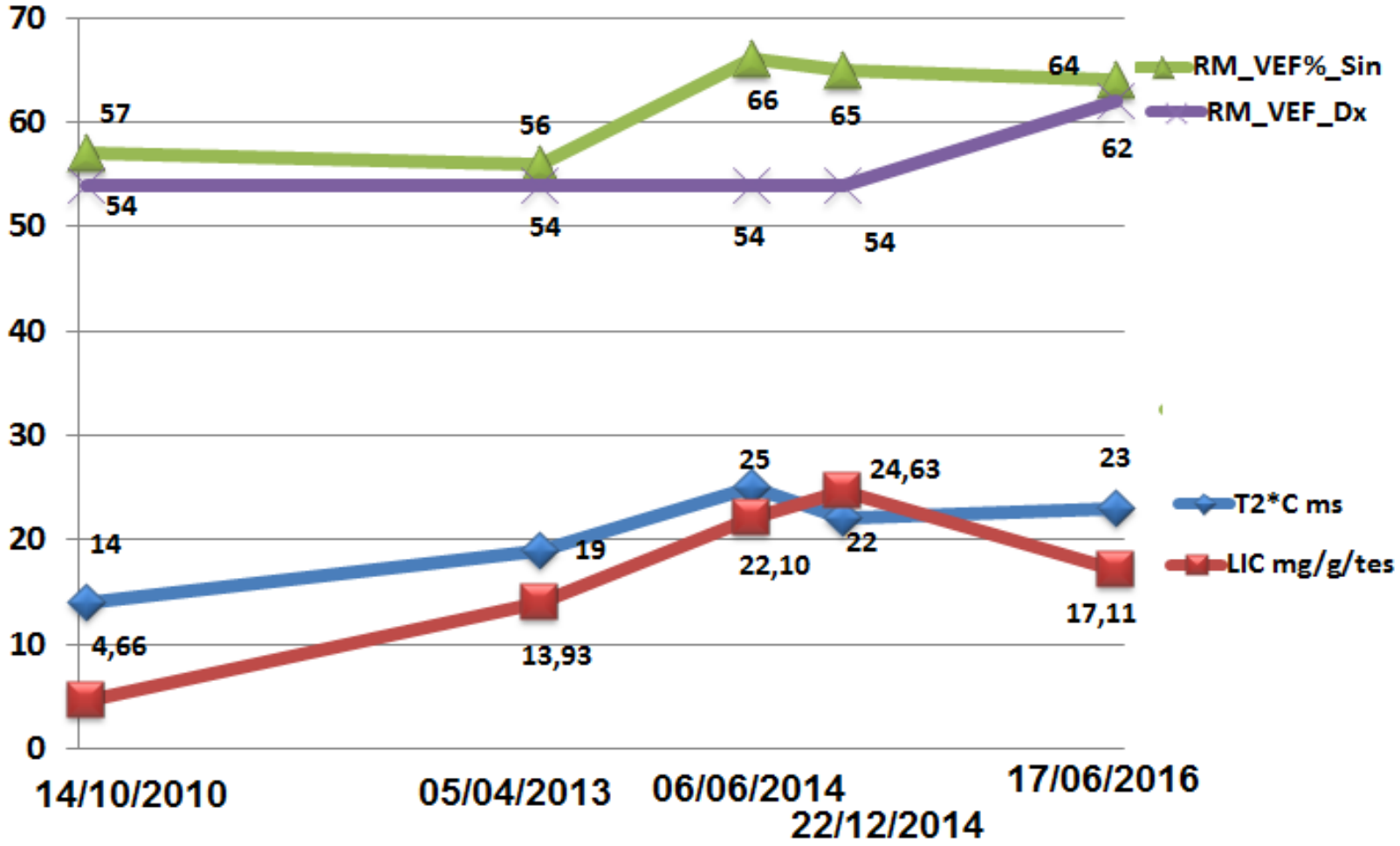
- **Neutropenia (2 episodi: 2003, 2012)**
- **Agranulocitosi (2012)**

DFX:

- **>Creatinina (monoterapia, 2006)**
- **concomitante > ALT (monoterapia,2009)**
- **> creatinina (2014, alternata 10mg/kg)**



Caso 4c : paziente difficili da trattare



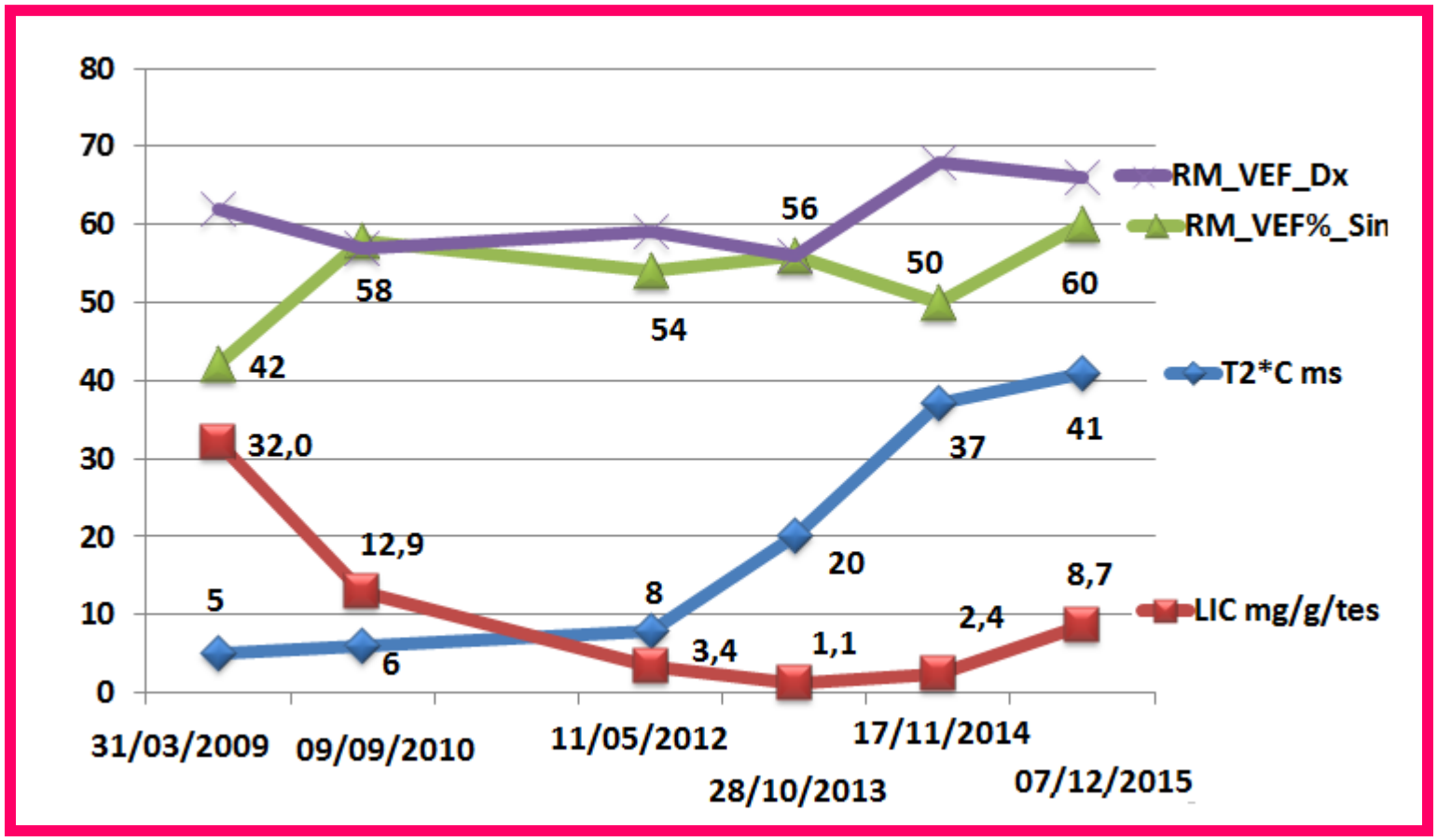
caso 5a: Terapia di associazione combinata DFO-DFP

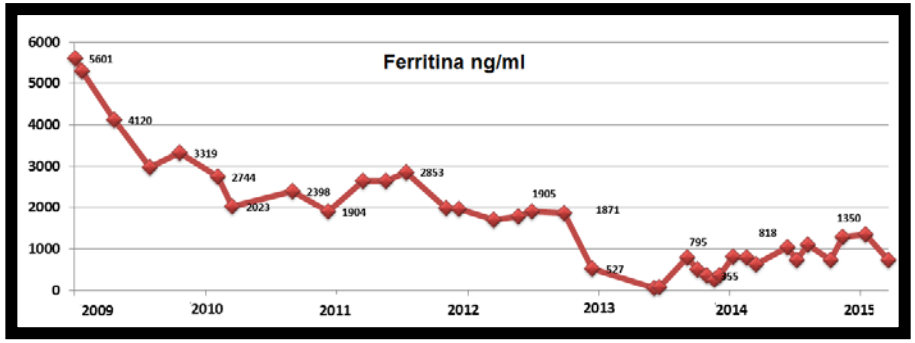
TM; M,46 anni (BM, 1970)
- Prima visita: maggio 2009
- Ricovero qualche mese prima per scompenso cardiaco
- RM: depositi elevati fegato cuore
- Ferritina 700 ng/ml
- DFO: 58 mg/kg 4/7

- Ferritina: 5601 ng/ml
- RM: T2* C 5ms, FE Vsx 42%; LIC: 31,95 mg/gtes
- Iron intake:0,45 mg/kg die
- Ipoparatiroidismo (2010)
- OGTT: diabete (insulina dal 2012)
- Ipogonadismo puberale
- Ipotiroidismo (2012)
- Osteoporosi
- Calcolosi colecistica
- Splenomegalia e lieve ipersplenismo
- Calcificazioni endocraniche e testicolari

Terapia chelante:
- DFO 56 mg/kg 6/7 + DFP 75mg/kg 7/7 dal 3/6/2009 al 1/12/2012
- DFO 56 mg/kg 4/7+ DFP 75mg/kg 7/7 fino al 14/10/2013
- DPO 100 mg/kg 7/7 fino al 1/1/2016
- DFP 100 mg/kg 7/7 + DFO 44 mg/kg 2-3/7

caso 5b: Terapia di associazione combinata DFO-DFP

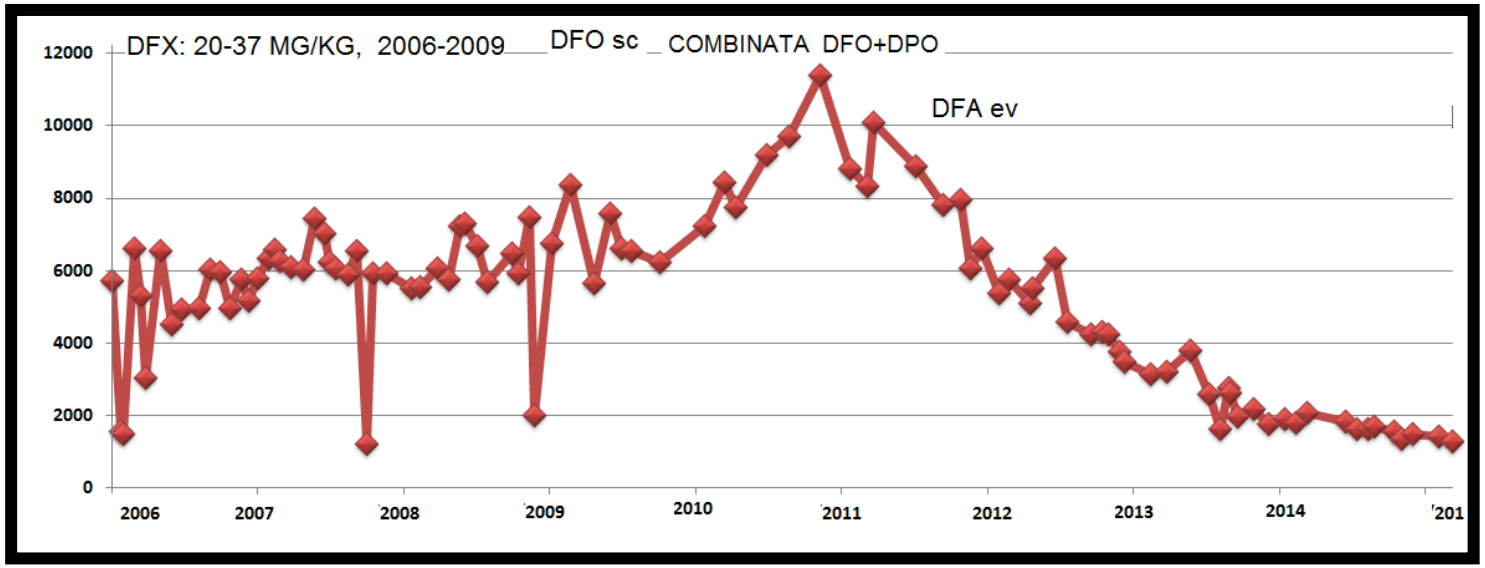




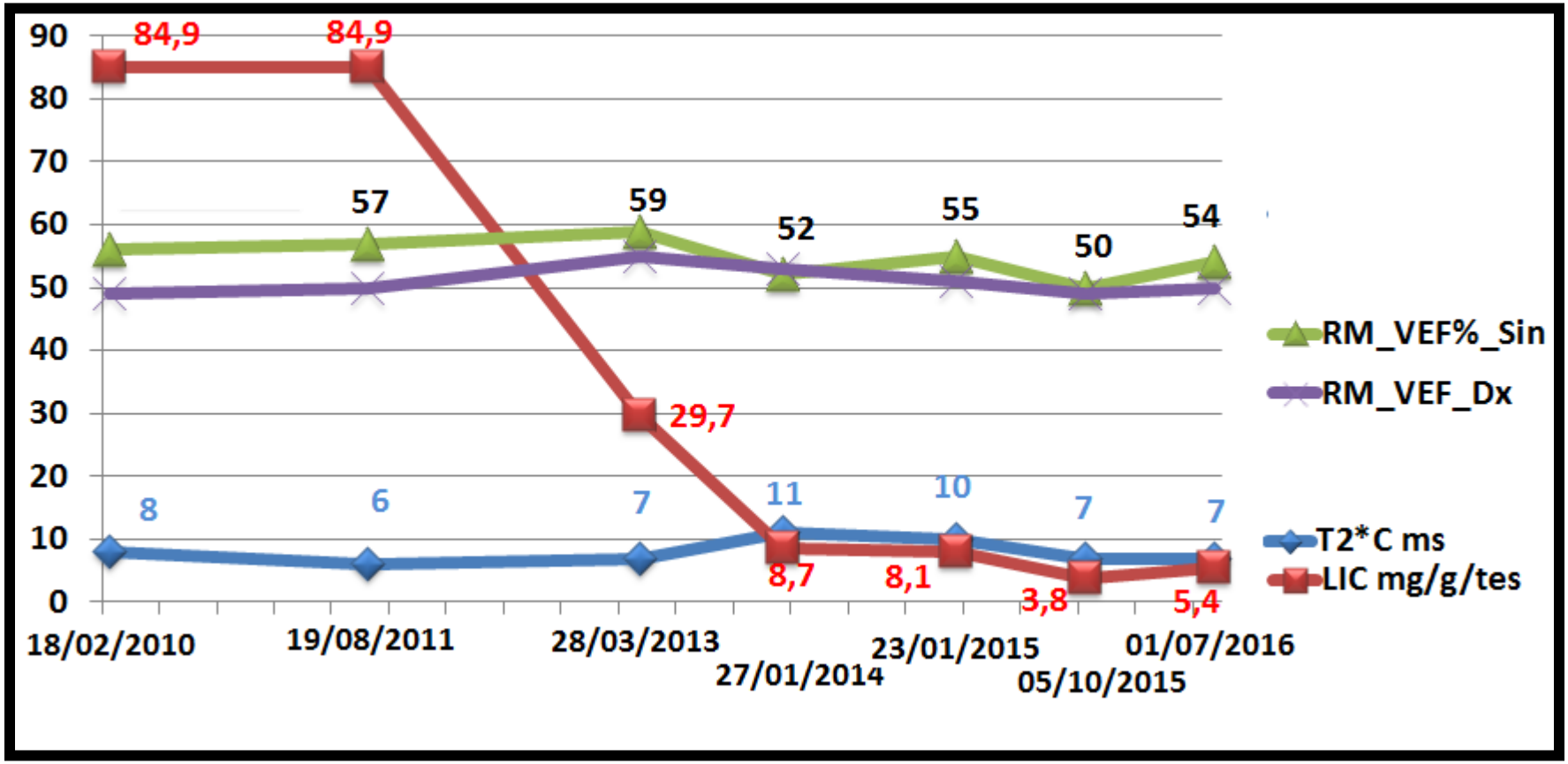
Caso 6a: terapia combinata e compliance

- TM; F, 39 anni (LFA,1977)
- Seguita dal 2006
- Scarsa compliance alla terapia chelante

- Splenectomia (2000)
- Amenorrea primaria
- Ipotiroidismo primario (2008)
- Diabete (2011)
- Fibrosi epatica avanzata (F3-F4 al primo Fibroscan del 2011)
- Nodulo epatico rigenerativo (2008)



Caso 6b: terapia combinata e compliance



Caso 7a: DFX in monoterapia e cardiopatia siderotica

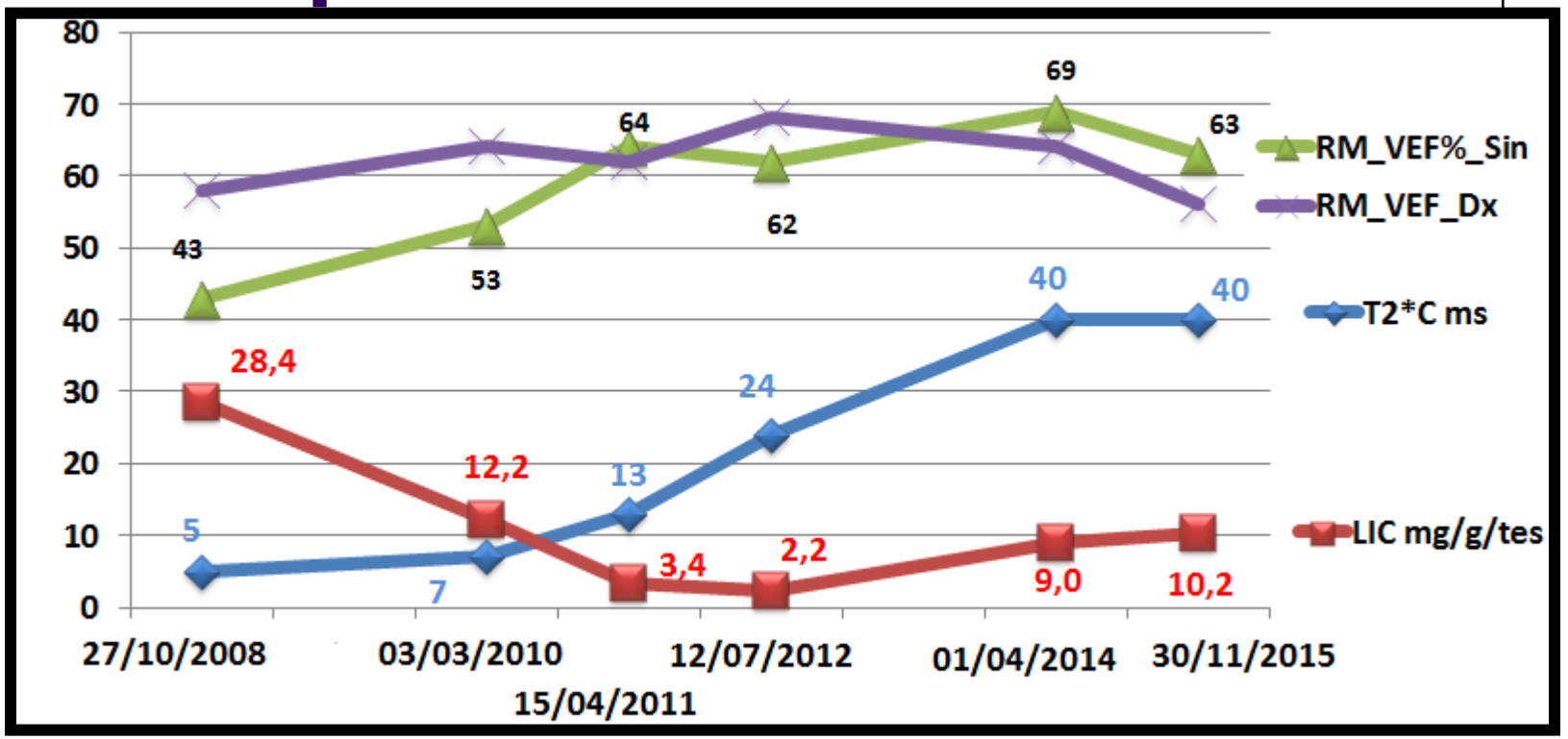
TM; M, 34 anni (MK,1982)
seguito dal 2009

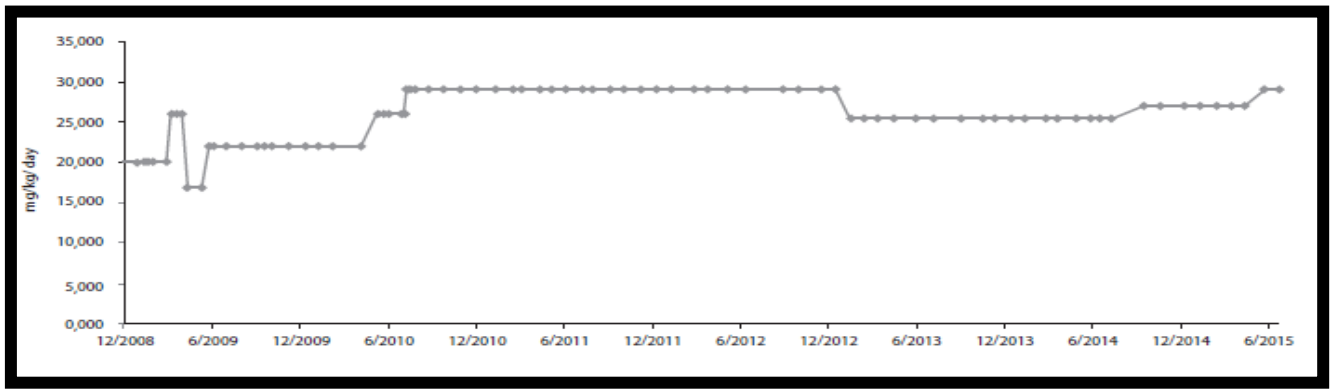
- **emosiderosi epatica e cardiaca**
- **cardiomiopatia siderotica con scompenso cardiaco nel dicembre 2007**

- **Epatite cronica HCV G1b (F3 alla BE del 2006)**
- **relapser PEG-INF (2007)**
- **Ipogonadismo puberale**
- **ipoacusia neurosensoriale bilaterale a 4000 Hz, stabile**
- **appendicectomia (2003)**
- **colecistectomia per calcoli (2006)**

Terapia chelante
DFO: 50 mg/kg 6-7/7
DFP: in associazione al DFO via orale non tollerata per nausea e vomito.

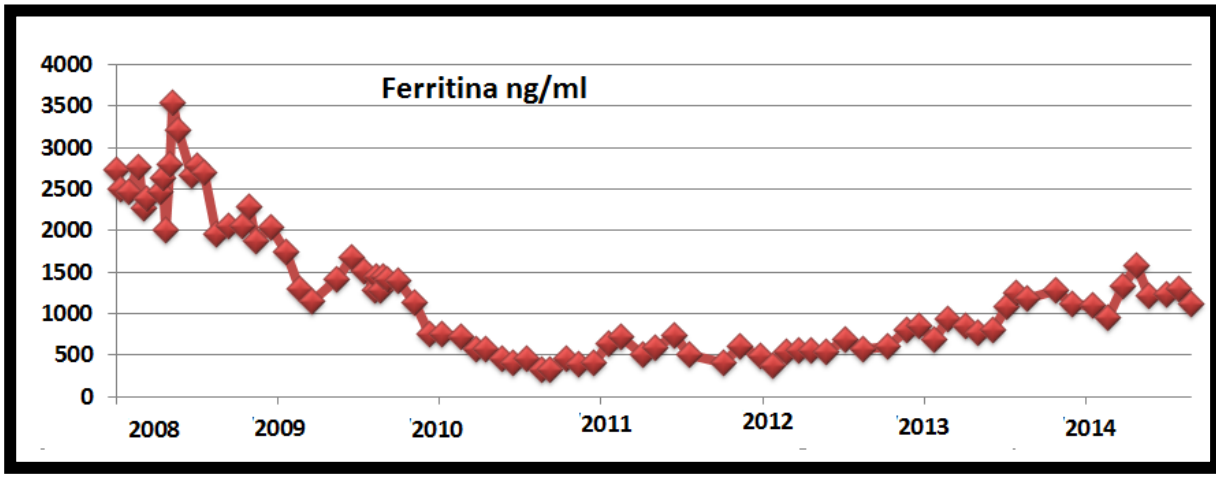
Caso 7b: DFX in monoterapia e cardiopatia

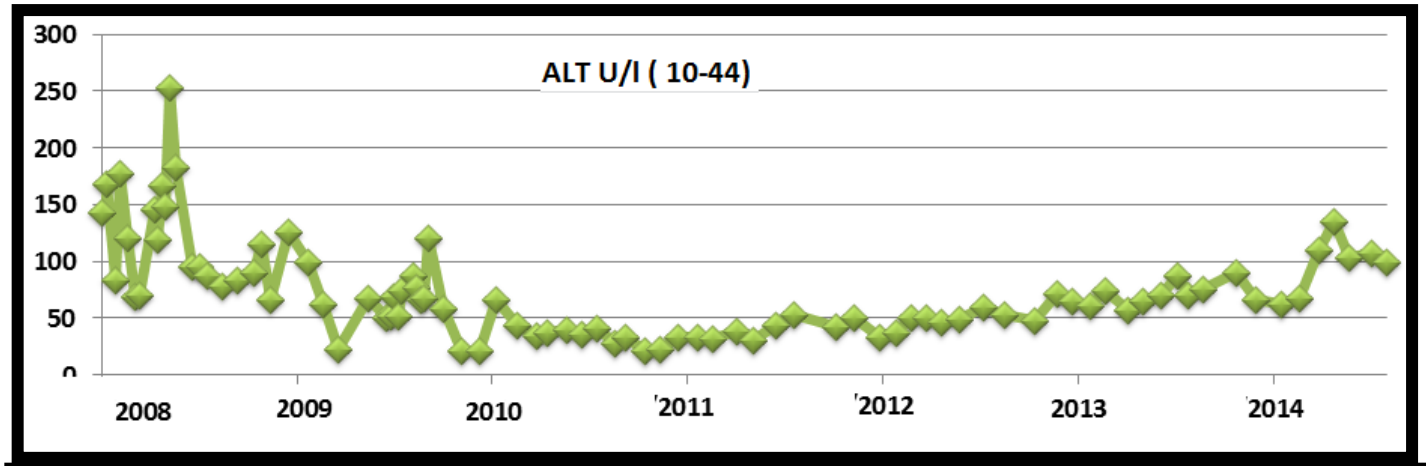


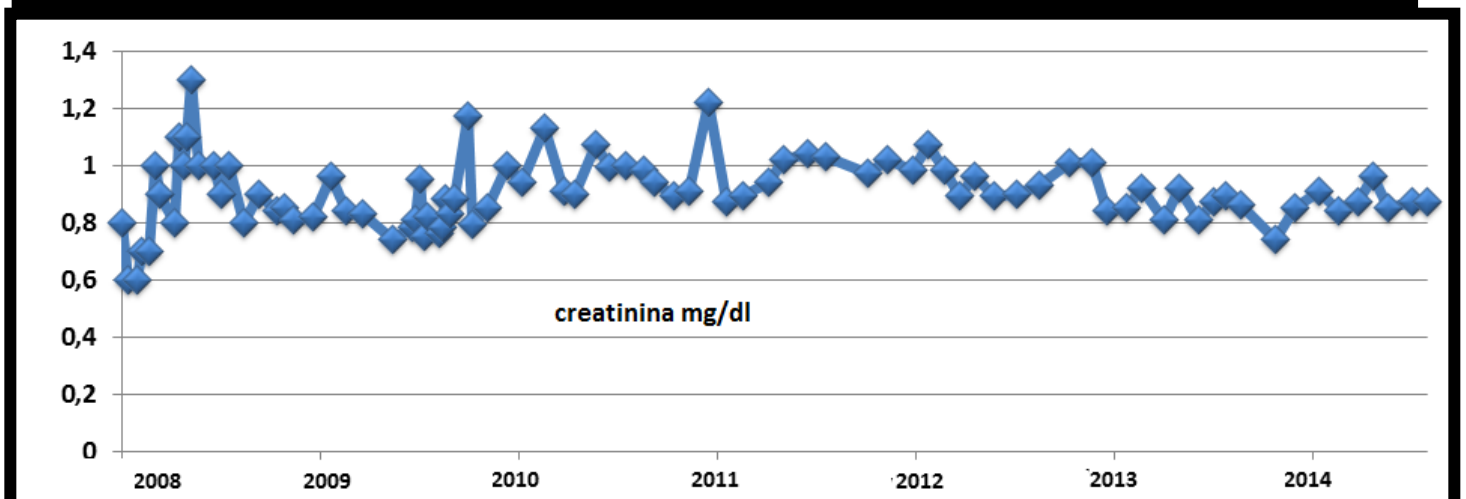


DFX dosaggio

Caso 7c:


Ferritina ng/ml
4000
3500
3000
2500
2000
1500
1000
500
0
2008
2009
2010
2011
2012
2013
2014


ALT U/l (10-44)
300
250
200
150
100
50
0
2008
2009
2010
2011
2012
2013
2014


creatinina mg/dl
1,4
1,2
1
0,8
0,6
0,4
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0
2008
2009
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2012
2013
2014

Conclusioni

- Gestione della terapia chelante: medico esperto o dedicato
- Scelte e cambiamenti di terapia: razionale, documentati nella storia clinica del paziente per le scelte future
- Pazienti problematici
- Importanza della adesione alla terapia

Ringraziamenti

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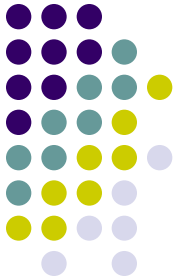
- Giovanni
- Patrizia Farina

- Tutti gli specialisti

- ALT : associazione dei pazienti

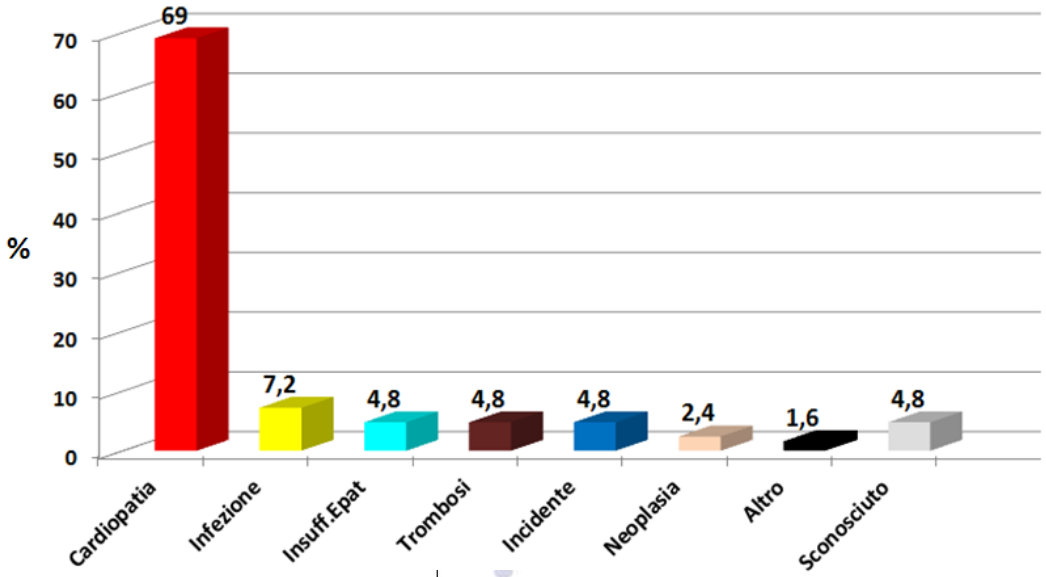
La storia della talassemia a Ferrara

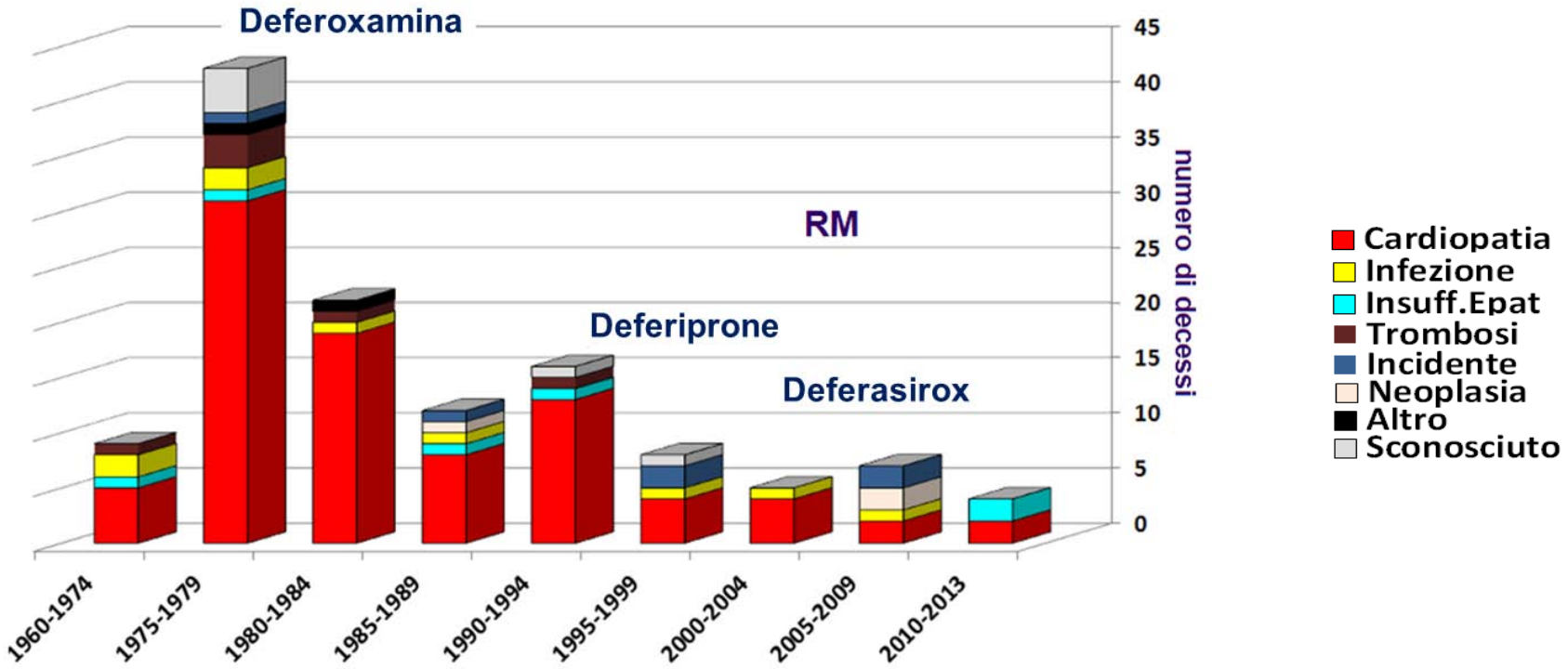


Grazie per l’attenzione

cause di morte da cardiopatia

(126/ 283 casi)





Terapia chelante

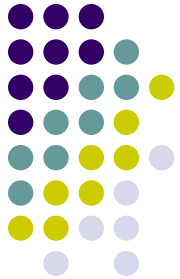
Monoterapia

- DFO sc , DFO ev, DPO, DFX

Associazione

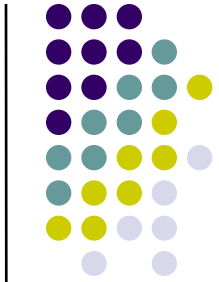
- DFO + DPO
- DPO + DFX
- DFX + DFO

Scelta del regime di chelazione



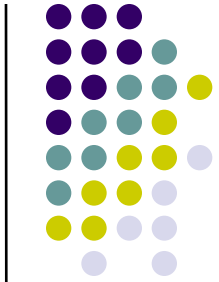
- Norme di prescrizione
- Età del paziente
- Entità dei depositi di ferro
- Entità del ferro introdotto
- Tossicità del farmaco
- Presenza di altre complicanze cliniche
- Presenza di altre terapie in corso
- Adesione alla terapia
- Qualità di vita

Monitoraggio della terapia chelante



- Efficacia
- Tossicità
- Adesione alla terapia: colloqui individuali

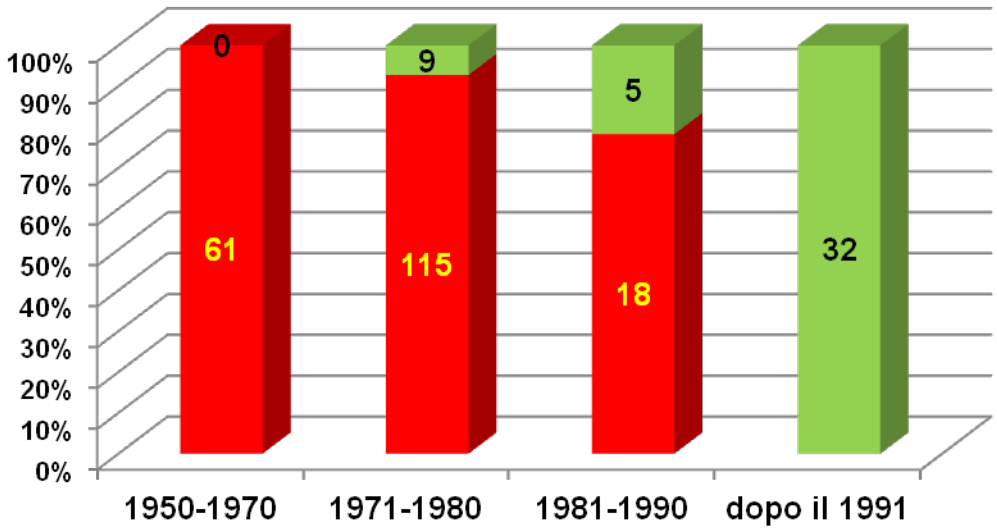
Valutazione dei depositi di ferro



- Dosaggio della ferritina serica

- Valutazione quantitativa dei depositi di ferro

HCV-Ab e anno d'inizio della terapia trasfusionale (240 casi)



HCV Ab pos 81%

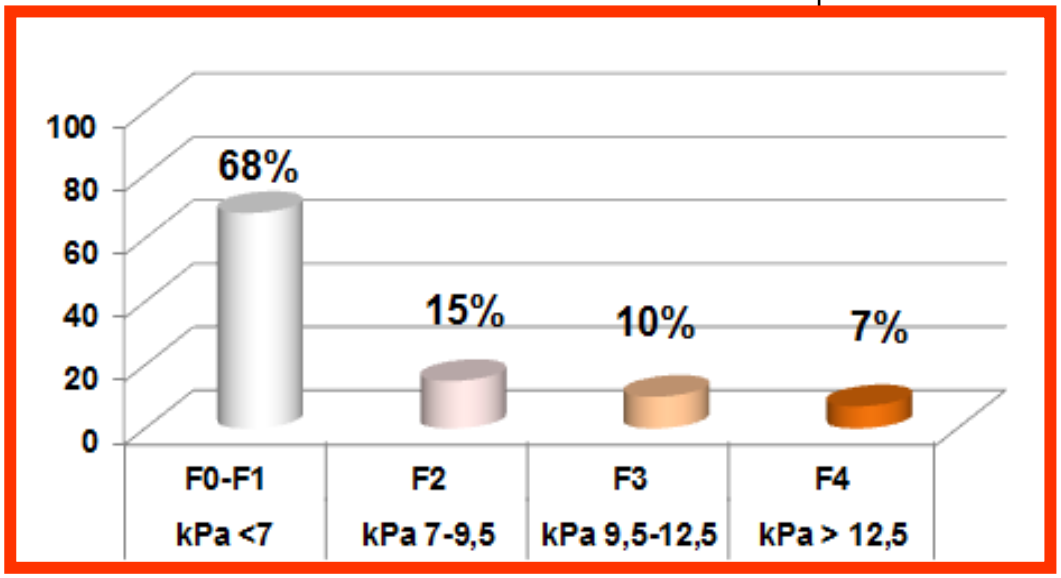
Prevalence of HCV-Ab positivity in thalassemia (Europe)

	Country	Patients	HCV-Ab pos
Wonke, 1990	GB	73 (1-39 yrs)	23,2%
de Montalembert, 1992	France	305	30%
Capocardo, 1992	Italy	152	47%
Resti, 1992	Italy	78	83,3%
Angelucci, 1994	Italy	256	60%
Prati, 1998	Italy	1481	80,2%
Cristofidou, 2000	Greece	122 (8-30 yrs)	61,4%

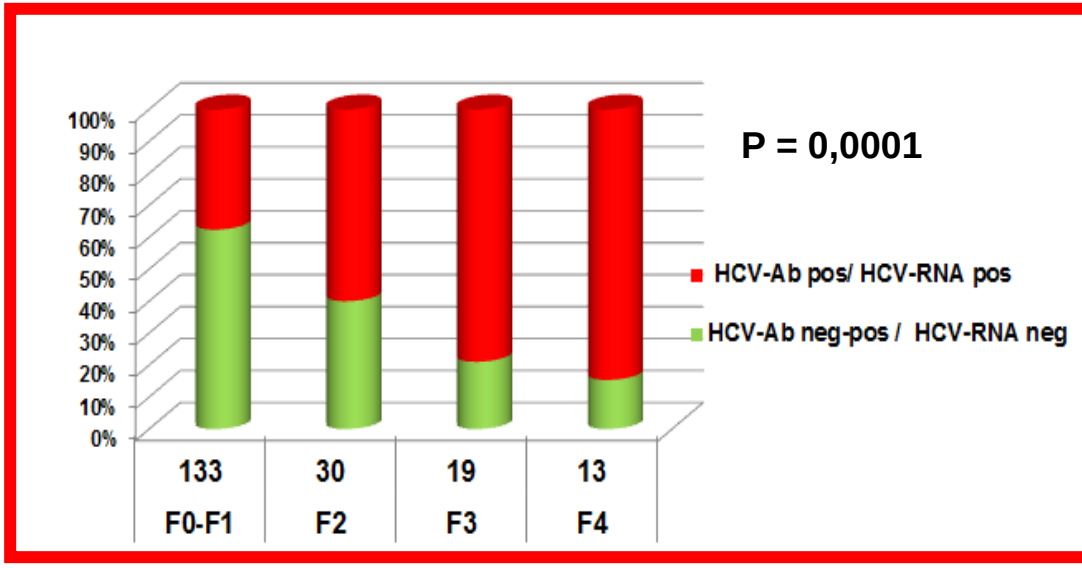
Elastografia epatica (fibroscan)

Misurazione attendibile: 195/214 (91%)

Pazienti	195
M/F	87/108
Diagnosi	TM:177; TDTI:18
ETA' aa (M ± DS)	38,4 ± 6,8 (18-55)
HCV-Ab neg	29 (15%)
HCV-Ab pos	166 (85%)
HCV-RNA pos	94 (57%)
HCV-RNA neg	72 (43%)
LS, kPa	5,8 (95%IC:5,4-6,3)

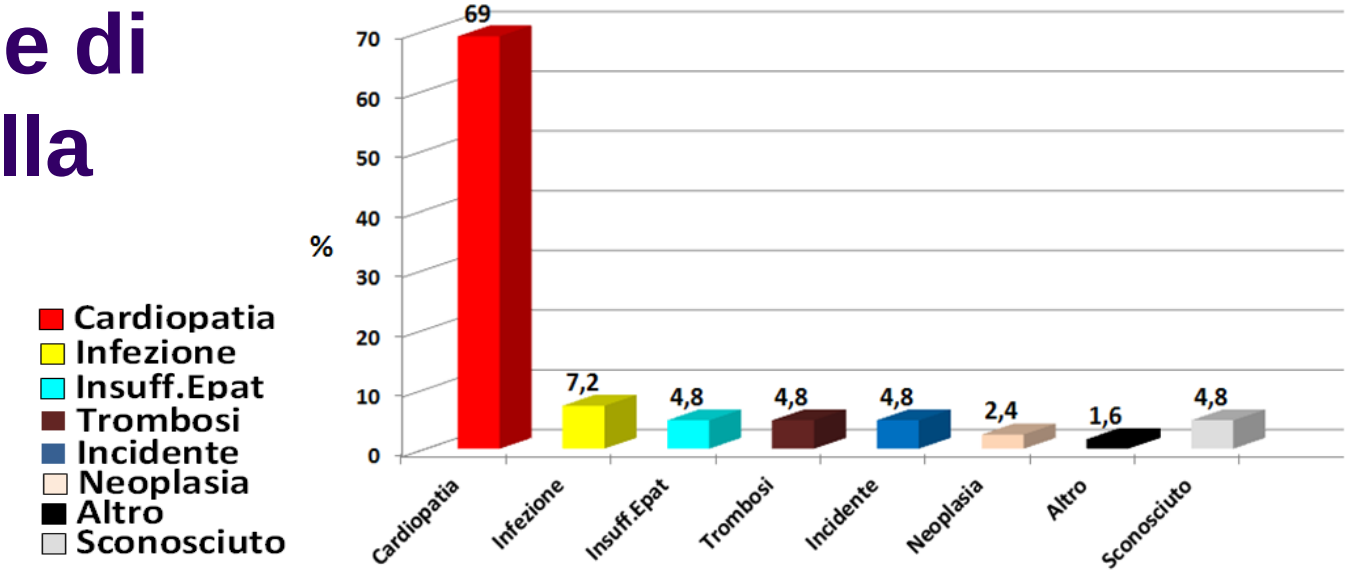


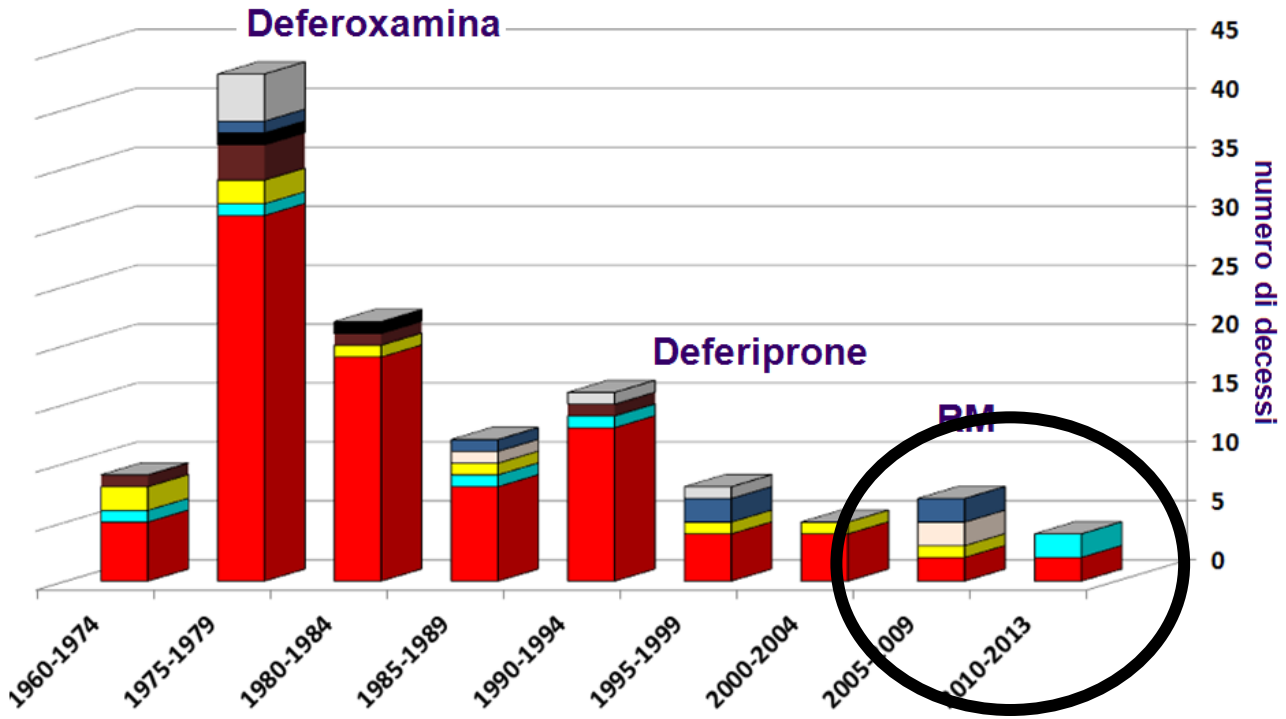
Castera et al, Gastroenetrology, 2005 Feb;128(2):343-50



HCV e cause di decesso nella talassemia

(126/ 286 casi)



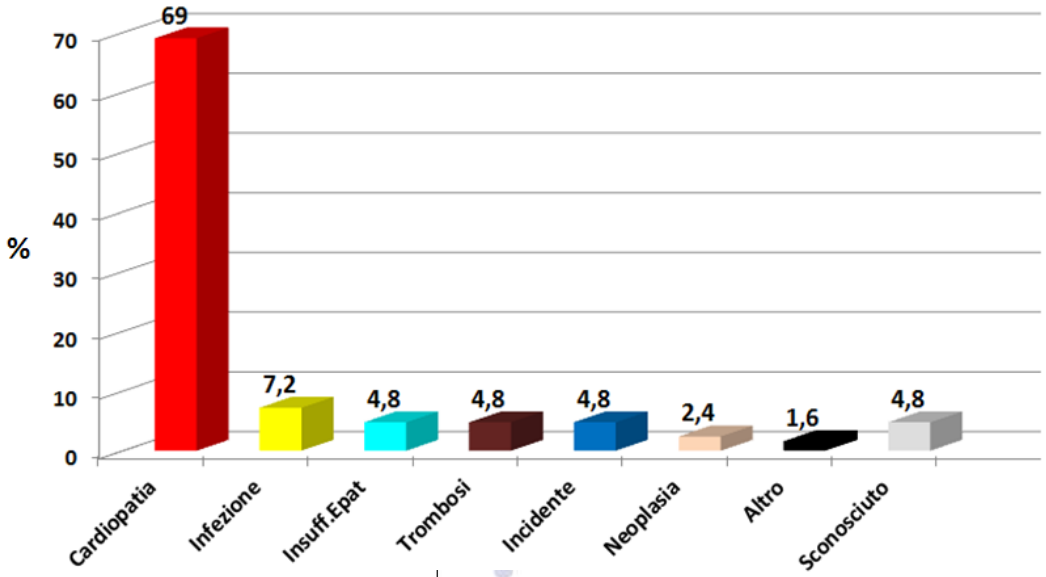


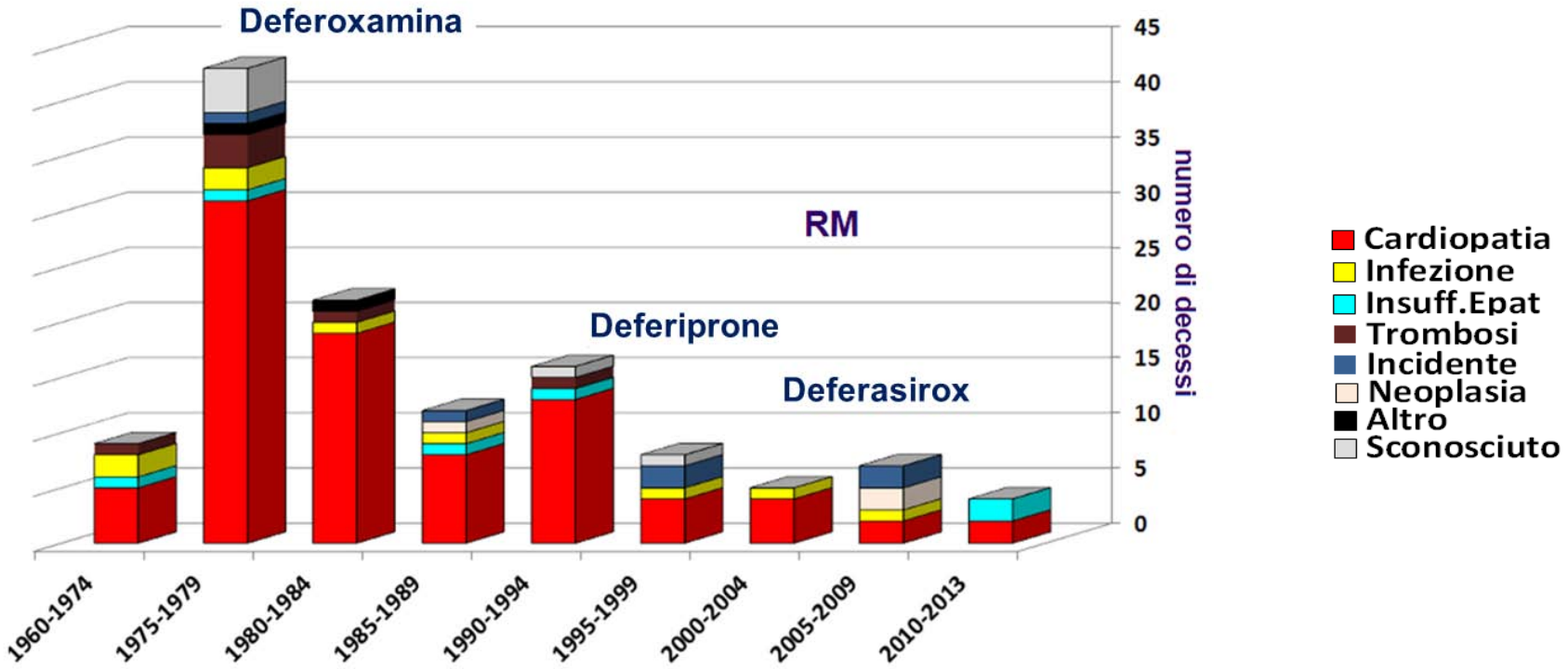
Dal 2005 al 9/2015
11 decessi
2 incidente

8/9 : HCV-RNA POS

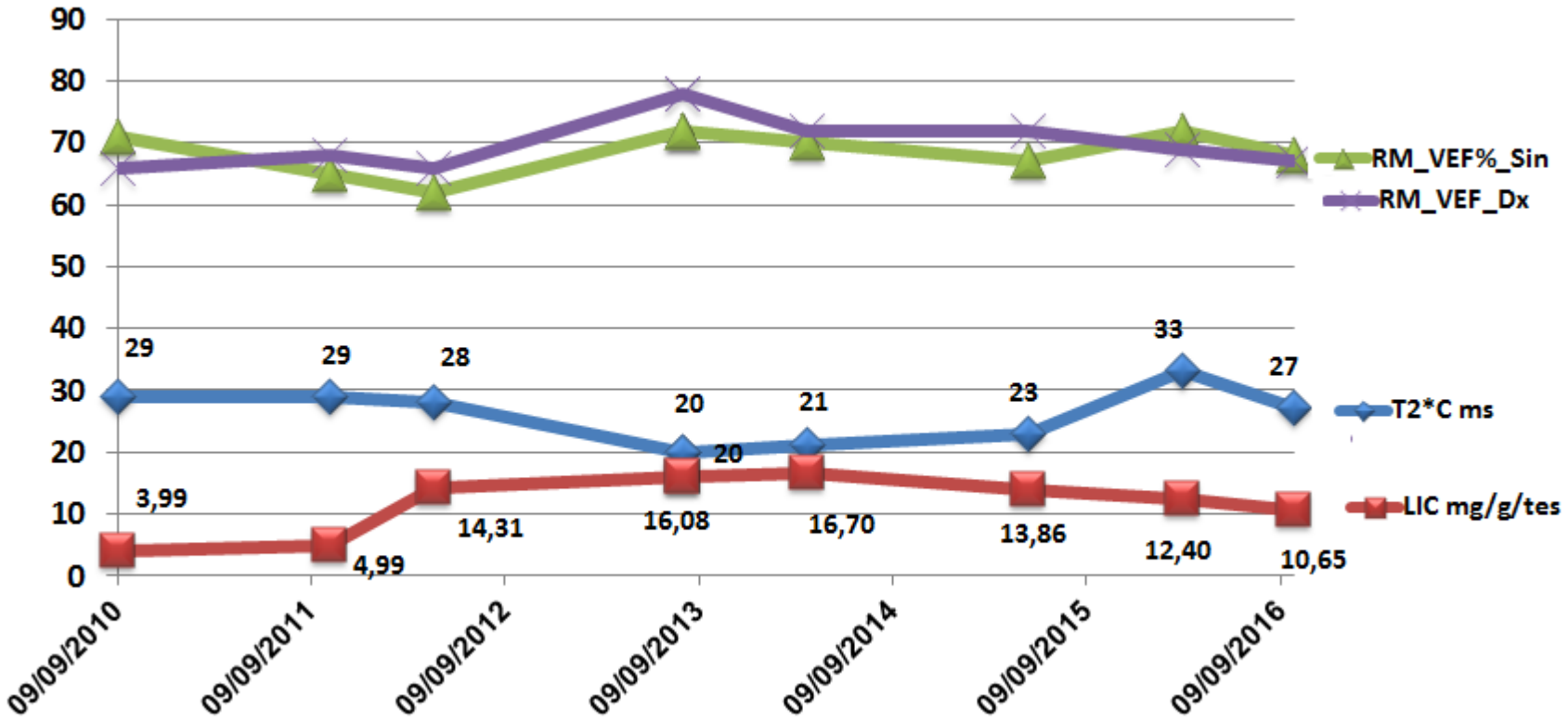
cause di morte da cardiopatia

(126/ 283 casi)

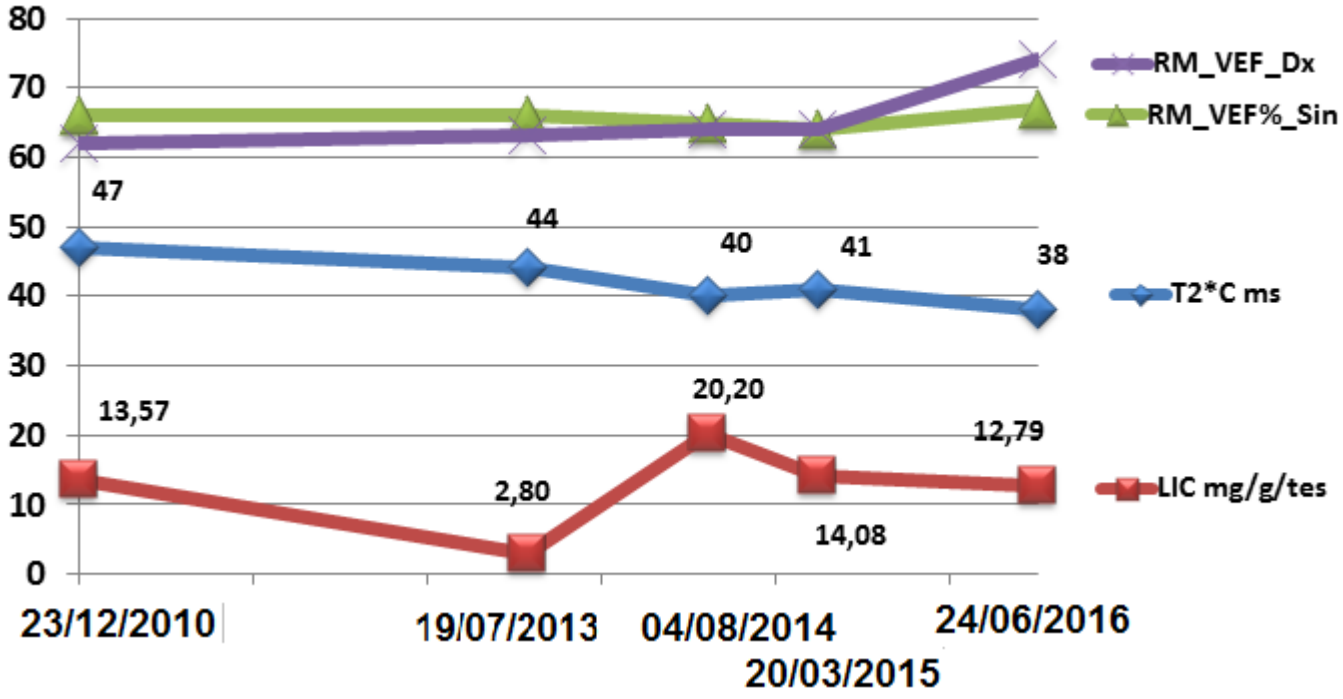




DFX VILLANI STEFANIA

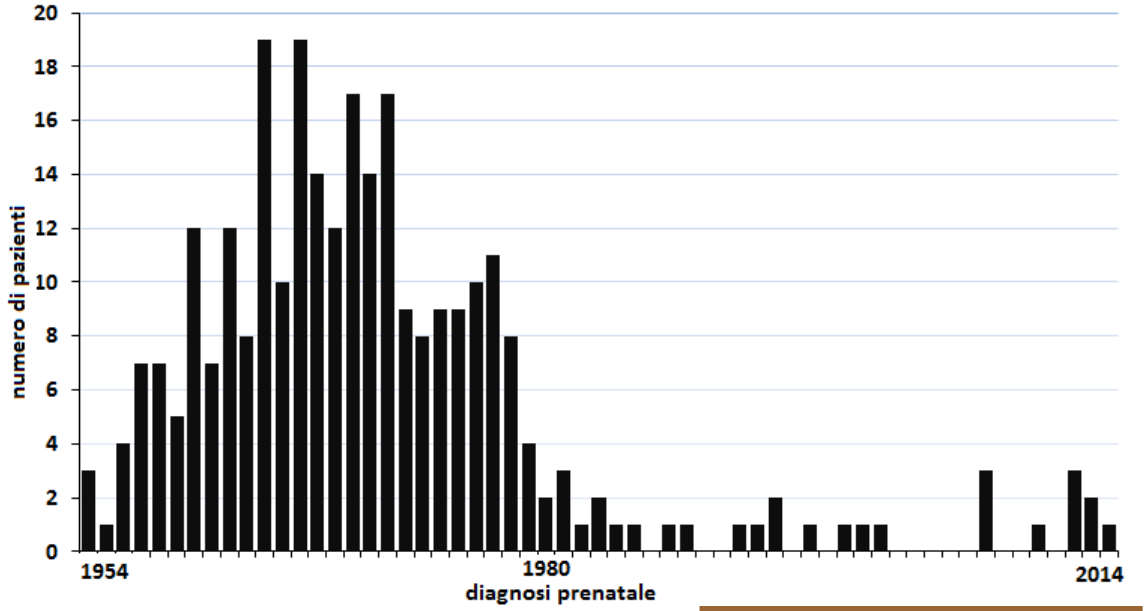


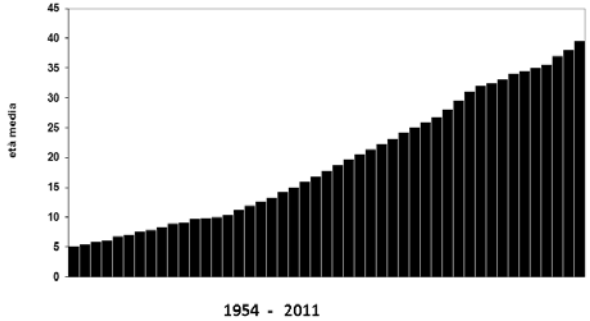
CASO 4: BARELLA KATY



286 pazienti con TM al 1/9/2015

- 10: persi al follow-up
- 16: trapianto di midollo
- 126: deceduti





ß-Thalassemia Major clinical features (*Thomas Cooley, 1925*)

- Impaired growth and development
- Bony abnormalities and facies
- Epatosplenomegaly
- Cardiomegaly
- Death within the first 6 years of life

ANALISI DI SOPRAVVIVENZA (KAPLAN MEIER) PER COORTE DI NASCITA IN 274 PAZIENTI CON ß-TALASSEMA MAJOR (2008)