



Associazione
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*Evidence of new techniques in
adjuvant radiation treatment of
gastric cancer*

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Chirurgia cardine di trattamento



Ruolo della linfadenectomia?

Significativo vantaggio di linfadenectomia più estesa:

Aumento OS a 5 anni

20,3% con D0, 41,2% D1 63,8% con D2

(Maruyama et al. Eur J Cancer, 1998)

D2 vs. D1: minore recidiva locoregionale tasso di mortalità inferiore Follow up a 15 anni su 1078mpz

(Songunet et al. The Lancet Oncology, 2010)

La sola chirurgia?

Incidenza di recidive locali del 60% nei pazienti >T2 e/o N+

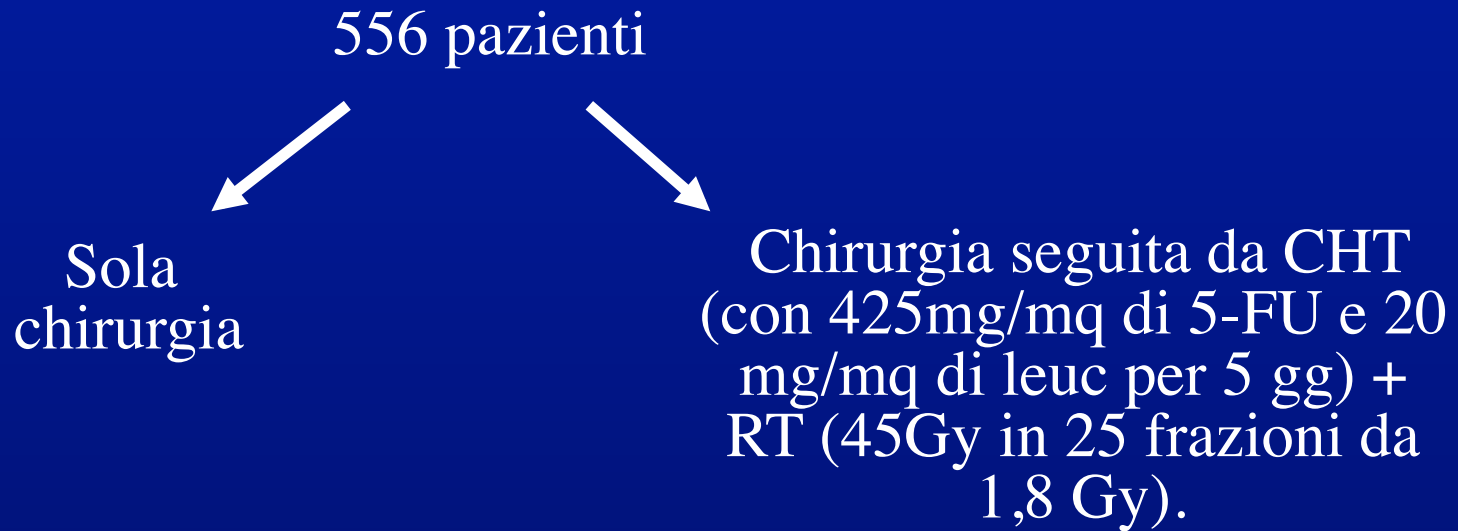
Necessità di terapia adiuvante

Dal 1969 diversi studi di CHT-RT adiuvante senza conclusioni definitive



Nessun miglioramento OS fino alla pubblicazione di INT-0116 che ha dimostrato miglioramento di OS e DFS (Macdonald et al. N Engl J Med 2001)

Trial INT-0116 :



Sopravvivenza a 3 aa 50% vs 41%; $P < 0,005$

Sopravvivenza a 5 aa 40% vs 28,4%; $P < 0,001$

OS 27 mesi vs 36 mesi; $P < 0,005$

Relapse free survival 31% vs 25%

Local regional relapse 29% vs 19%

Tossicità trial INT-0116

TABLE 3. MAJOR TOXIC EFFECTS OF CHEMORADIOTHERAPY.*

| TYPE OF TOXIC EFFECT | No. OF PATIENTS (%) |
|----------------------|---------------------|
| Hematologic | 148 (54) |
| Gastrointestinal | 89 (33) |
| Influenza-like | 25 (9) |
| Infection | 16 (6) |
| Neurologic | 12 (4) |
| Cardiovascular | 11 (4) |
| Pain | 9 (3) |
| Metabolic | 5 (2) |
| Hepatic | 4 (1) |
| Lung-related | 3 (1) |
| Death† | 3 (1) |

*Major toxic effects were defined as those of grade 3 or higher. Data are for the 273 patients who received chemoradiotherapy.

†One patient died from a cardiac event, one from sepsis complicating myelosuppression, and one from pulmonary fibrosis.

Tossicità significativamente più alta nel gruppo CHT-RT:

- $\frac{3}{4}$ hanno avuto una tossicità di grado 3-4
- 17% ha dovuto interrompere il trattamento

TERAPIA ADIUVANTE

Tali risultati hanno reso standard la radiochemioterapia adiuvante nel trattamento della malattia localmente avanzata (Stadio T3-T4 N+ o N-) negli USA.

**Chemioterapia
+
Radioterapia**
?

**Radioterapia
Conf. 3D**
?

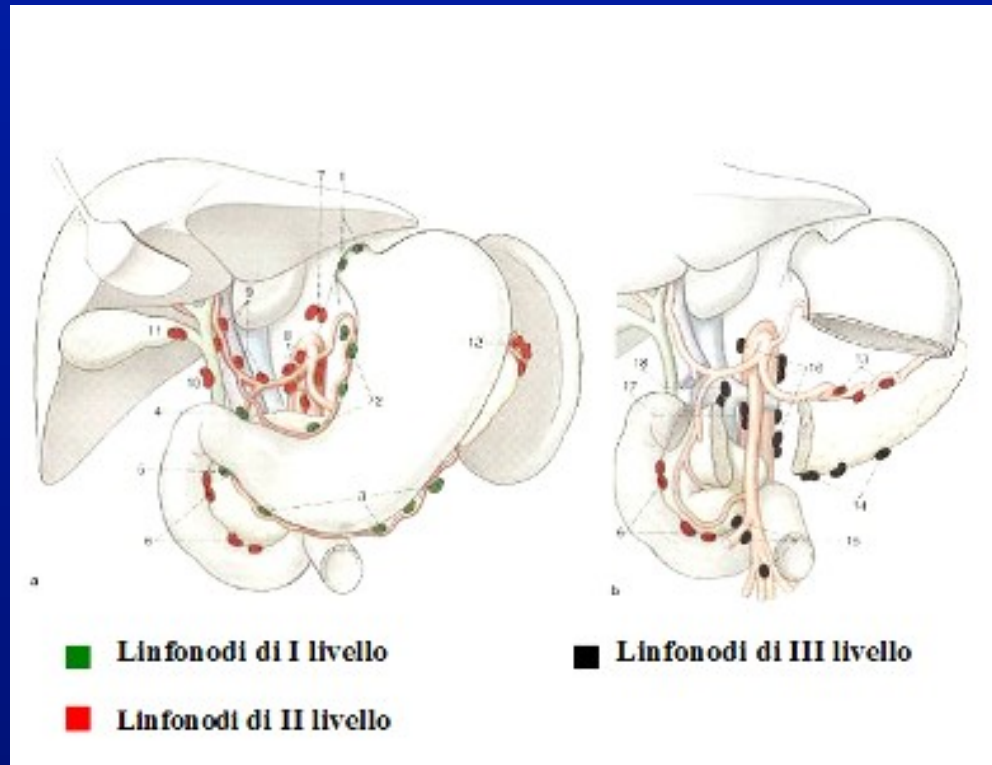
IMRT
?

Chemioterapia
?

Tomoterapia
?



Target



Importanza definizione dei volumi e delle stazioni linfonodali trattate in funzione della sede di T

Constraints

- Fegato: 60% del fegato deve ricevere <30 Gy
- Rene: $2/3$ di un rene deve ricevere <20 Gy
- Midollo spinale: <45 Gy

In passato si utilizzavano campi AP / PA che erano considerati la soluzione più pratica

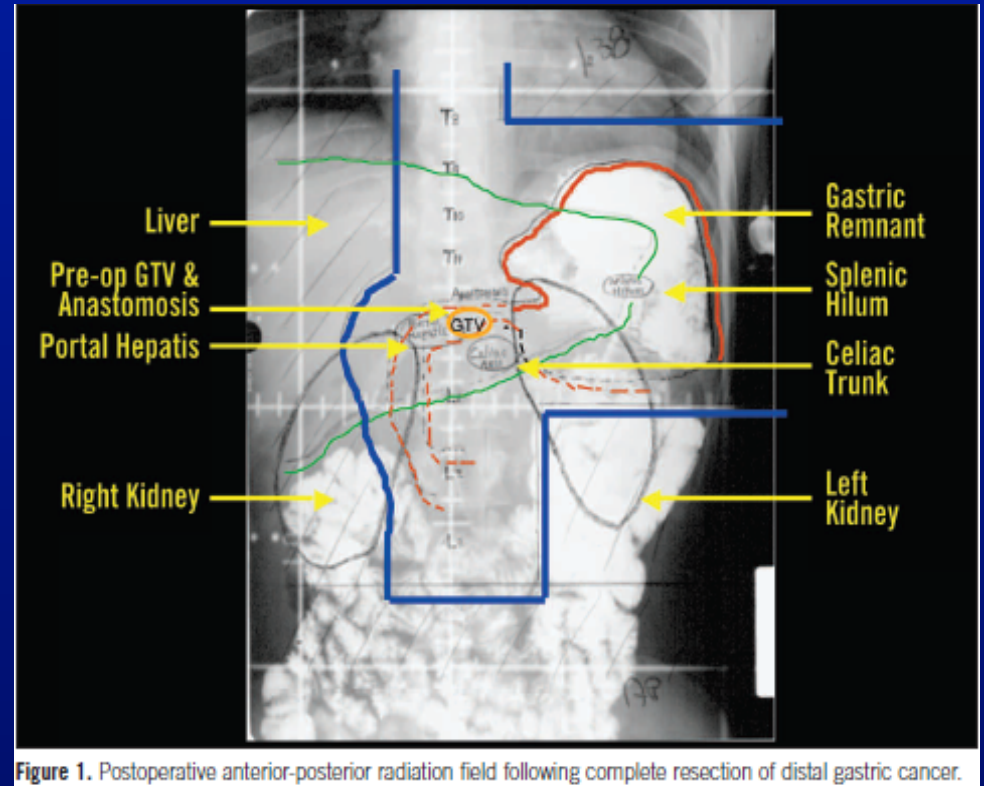
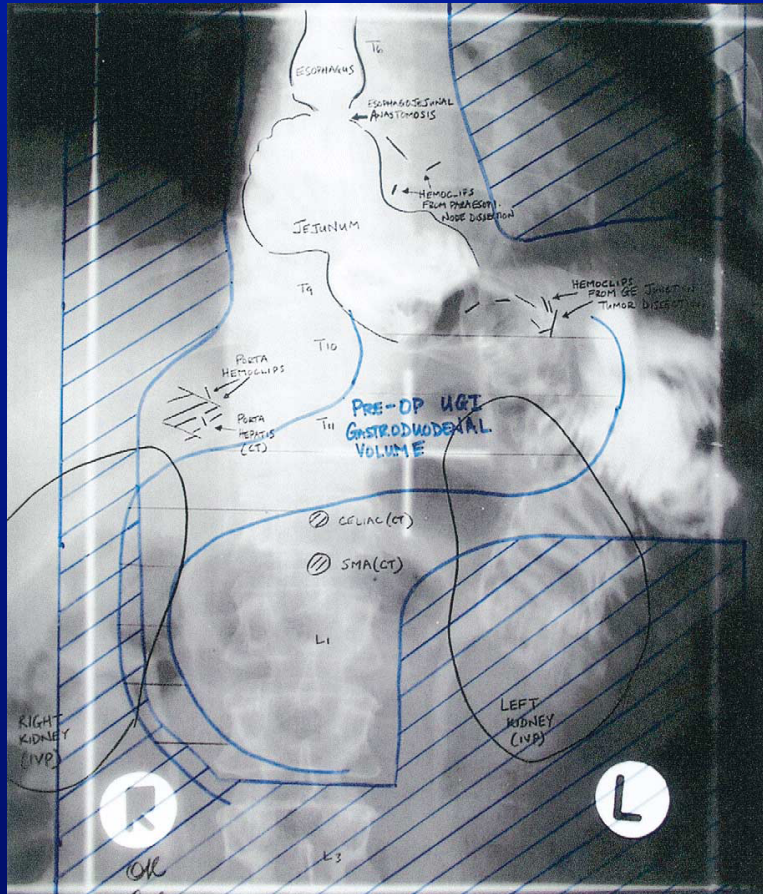


Figure 1. Postoperative anterior-posterior radiation field following complete resection of distal gastric cancer.

Ma la tossicità legata a questo tipo di tecnica era significativa per l'ampiezza del campo di trattamento

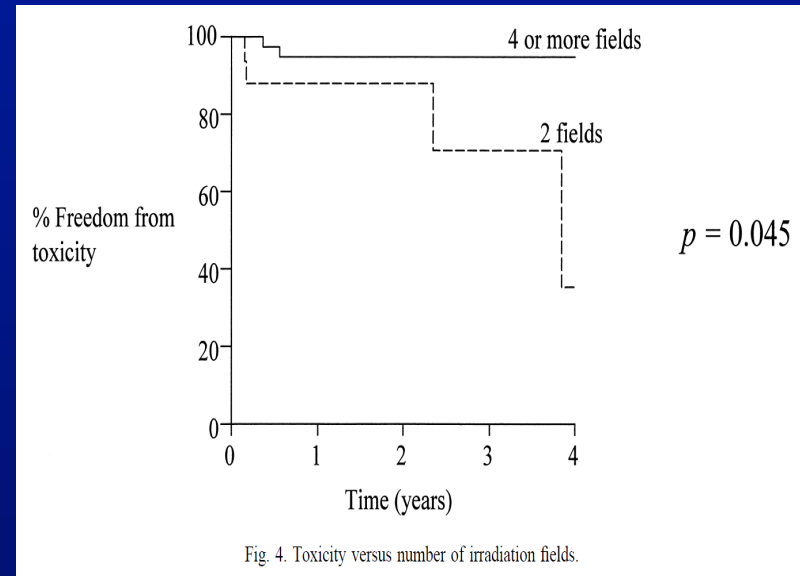
AP/PA vs 4-5 irradiation fields

Studio retrospettivo di 63 pazienti trattati con RT post-operatoria con o senza chemioterapia presso la Mayo Clinic tra il 1980 e il 1996

18 pazienti trattati con AP-PA, 4 (22%) tossicità di grado 4 o 5

vs

46 pazienti trattati con 4 campi, 2 (4%) tossicità di grado 4 o 5 ($p = 0.045$).



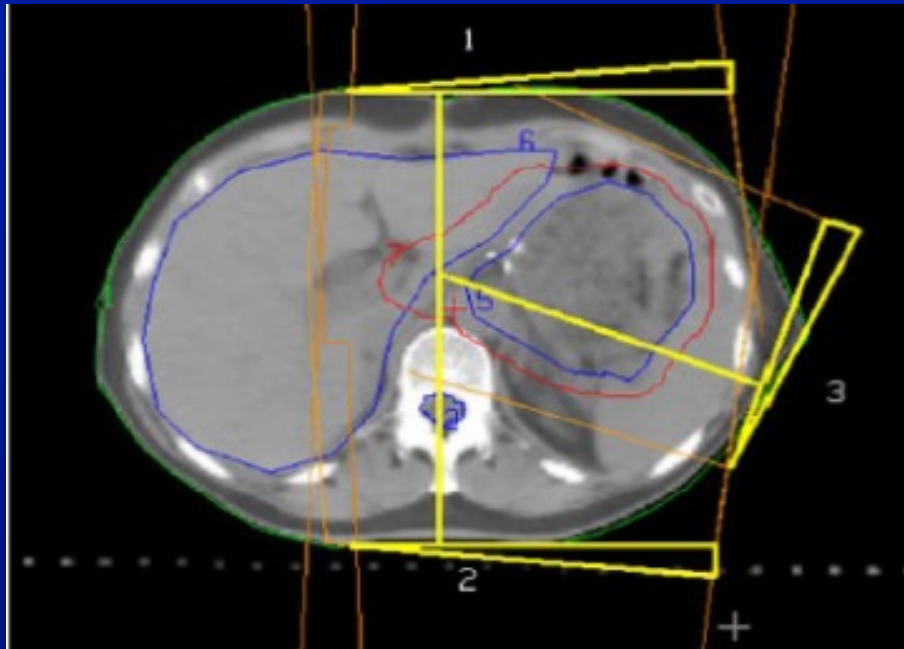
Henning GT et al: Results of irradiation or chemoirradiation following resection of gastric adenocarcinoma. *Int J Radiat Oncol Biol Phys* 46:589–598, 2000

STUDIO DOSIMETRICO: AP/PA vs 3D-CRT

3D Conformal radiotherapy for gastric cancer—results of a comparative planning study

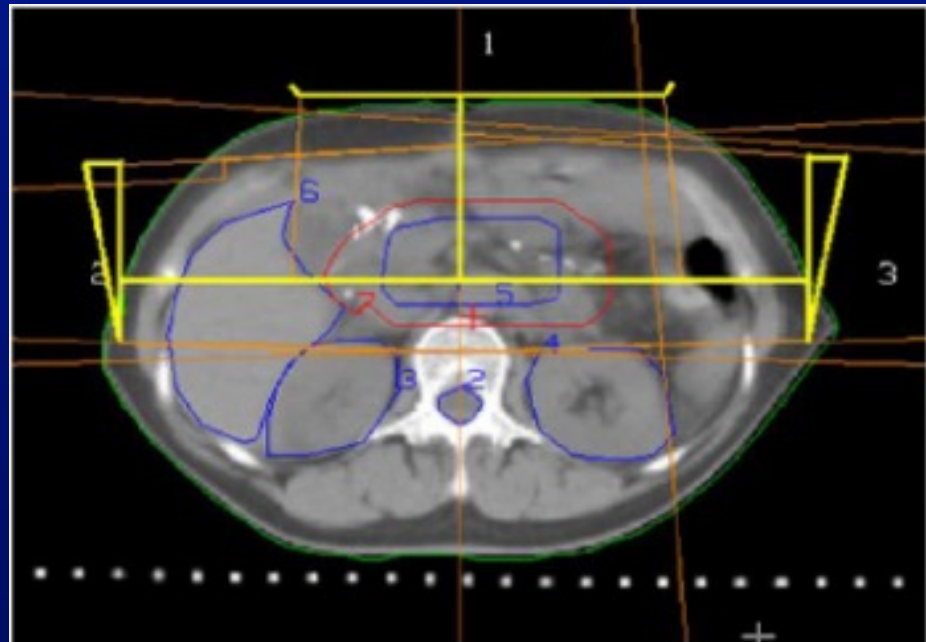
- 15 pz confronto piani AP/PA e 3D-CRT
- Inclusi pazienti con localizzazione del 1/3 medio o distale, con > 3 linfonodi positivi.
- Necessità di includere i LN perigastrici, celiaci, para-aortici, pancreatico-duodenali e del tripode celiaco con CTV ai limiti dei reni.

Tecnica split-field con PTV diviso in due sezioni ciascuna delle quali utilizza 3 campi differenti

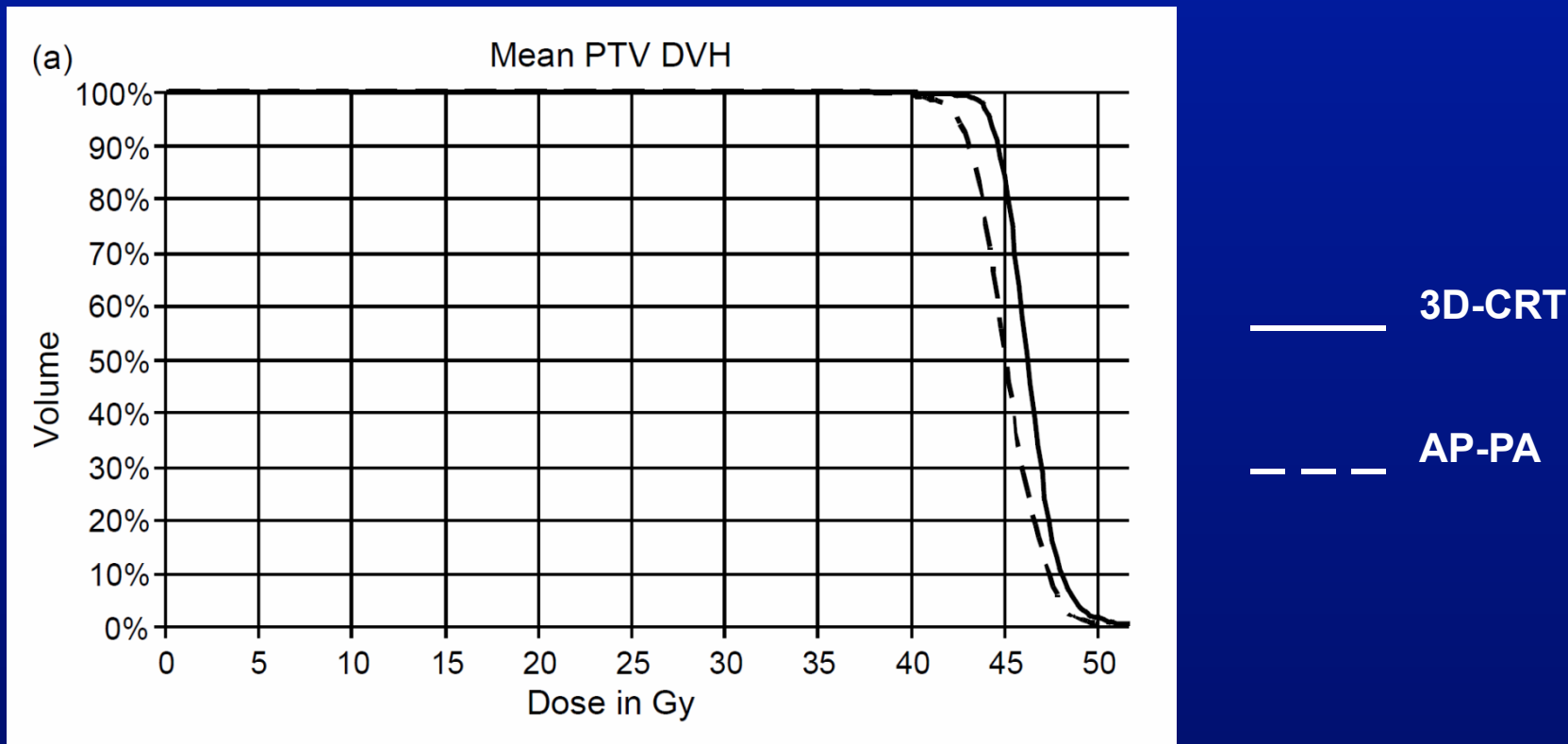


Metà superiore

Metà inferiore

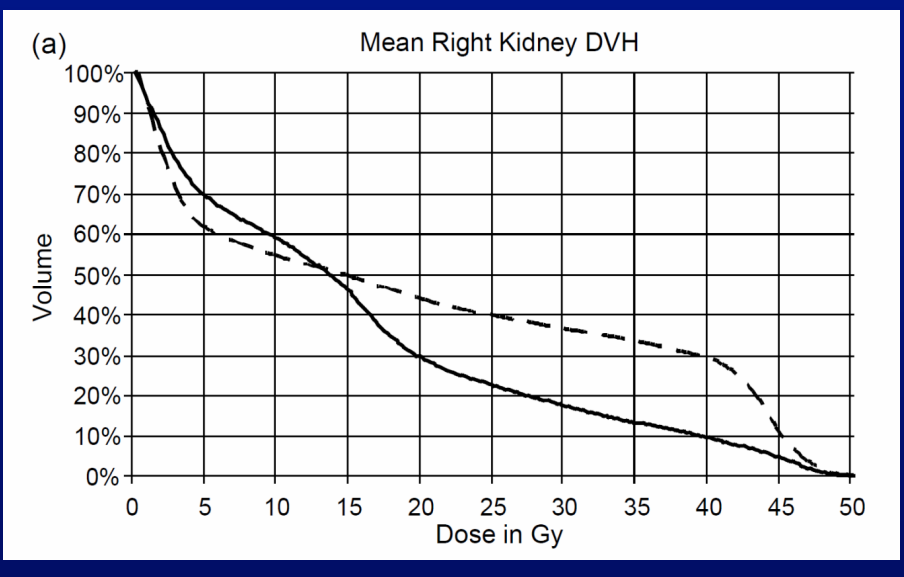
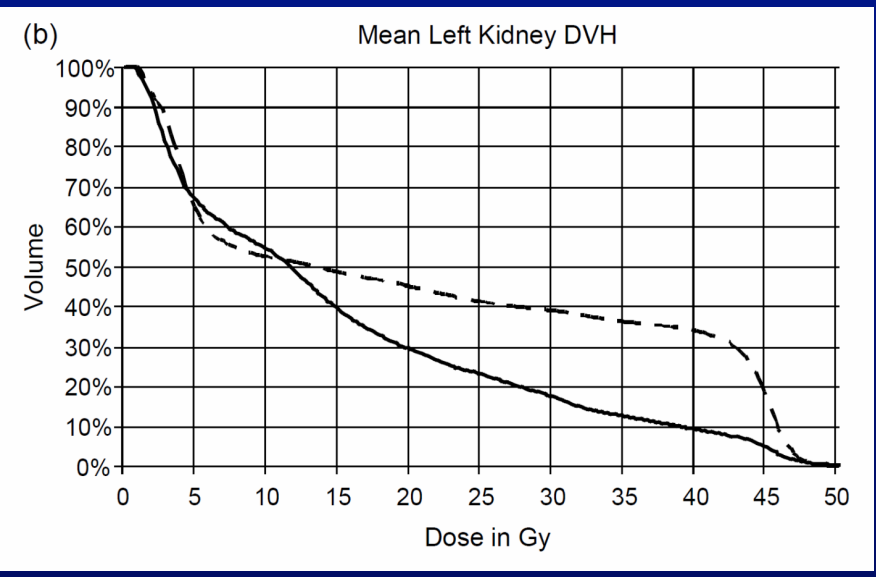
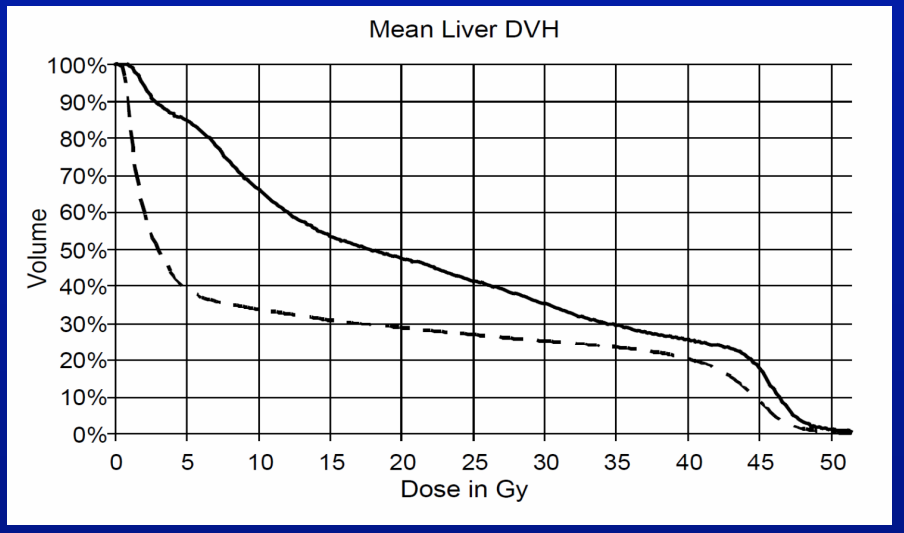
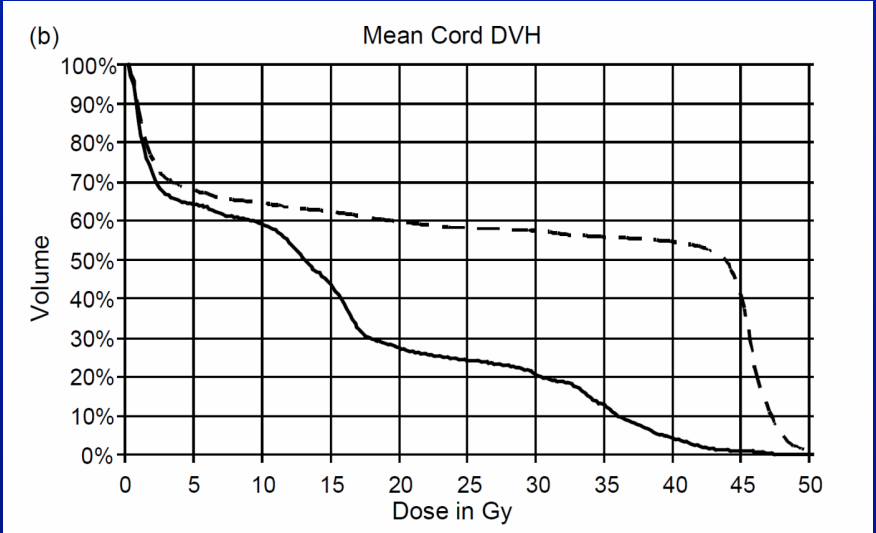


La 3D-CRT fornisce una migliore copertura del volume bersaglio.



Il 99% del PTV riceve il 95% della dose prescritta vs il 93% con AP-PA.

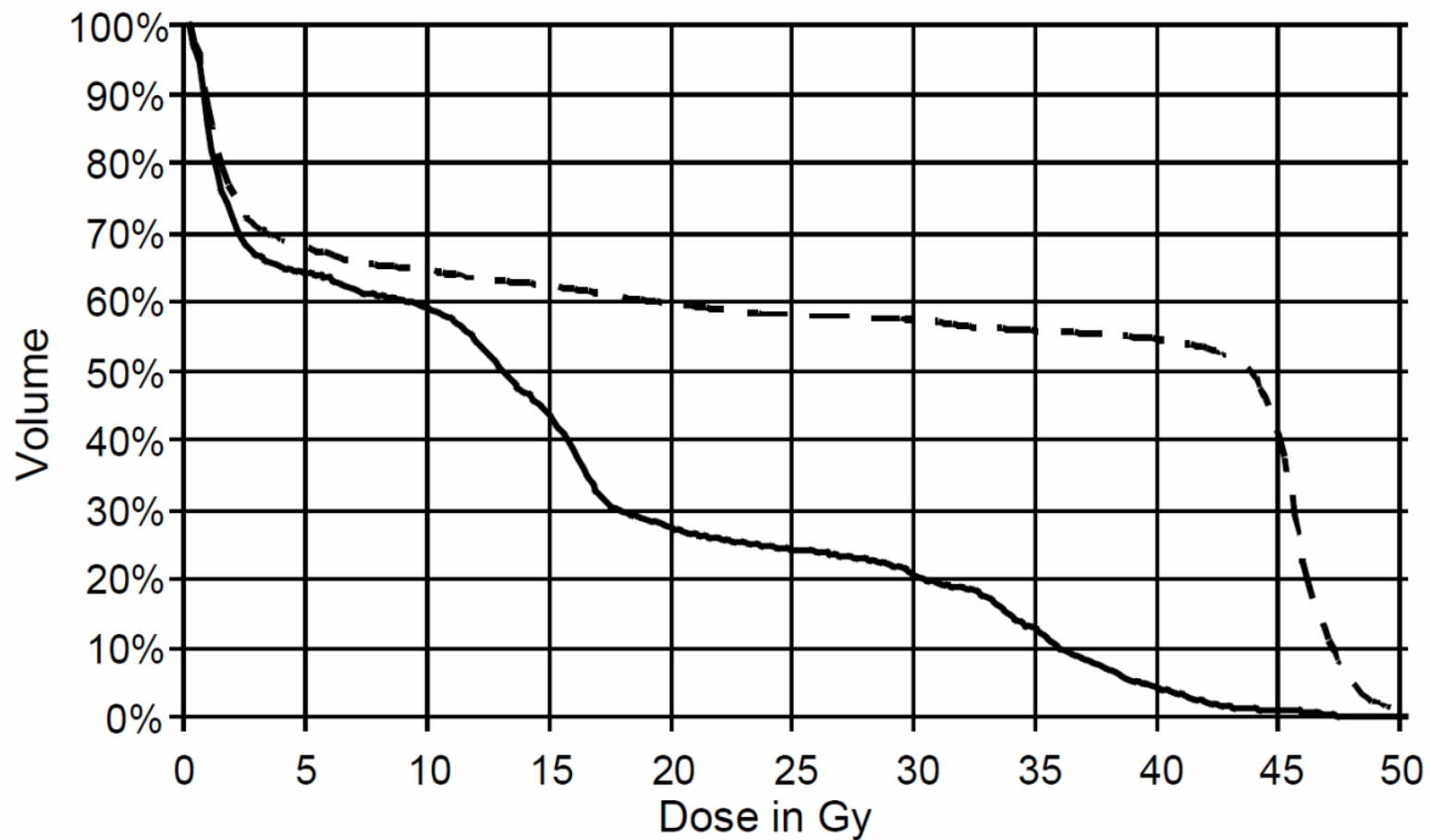
La percentuale del PTV che riceve il 98% della dose prescritta è 95% per la tecnica 3D-CRT vs il 71% della tecnica AP-PA



———— 3D-CRT - - - - AP-PA

(b)

Mean Cord DVH



—— 3D-CRT

- - - AP-PA



Impossibile visualizzare l'immagine. La memoria del computer potrebbe essere insufficiente per aprire l'immagine oppure l'immagine potrebbe essere danneggiata. Riavviare il computer e aprire di nuovo il file. Se viene visualizzata di nuovo la x rossa, potrebbe essere necessario eliminare l'immagine e inserirla di nuovo.



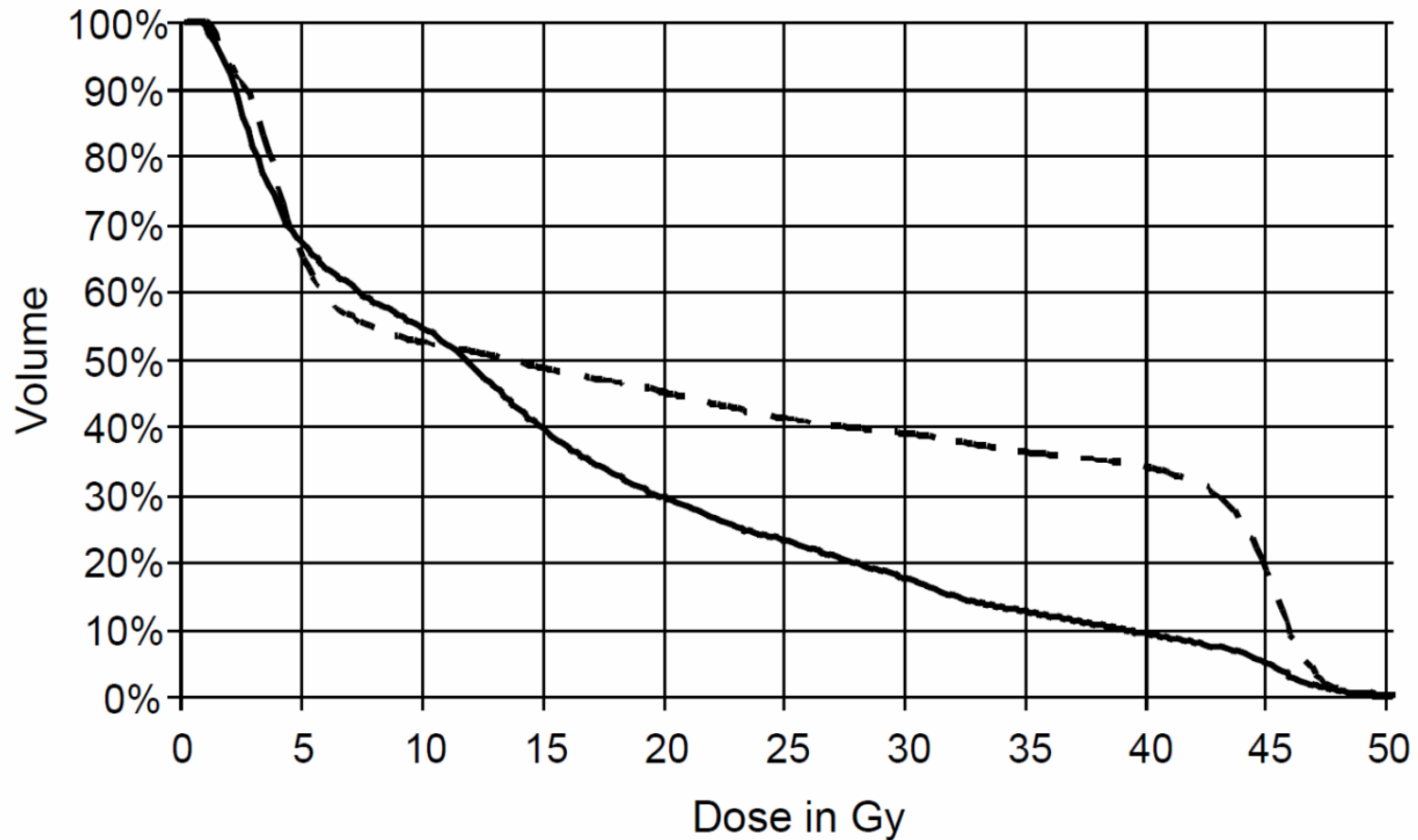
3D-CRT



AP-PA

(b)

Mean Left Kidney DVH



———— 3D-CRT

- - - - AP-PA



Impossibile visualizzare l'immagine. La memoria del computer potrebbe essere insufficiente per aprire l'immagine oppure l'immagine potrebbe essere danneggiata. Riavviare il computer e aprire di nuovo il file. Se viene visualizzata di nuovo la x rossa, potrebbe essere necessario eliminare l'immagine e inserirla di nuovo.



3D-CRT



AP-PA

STUDIO CLINICO 3D-CRT

Post-operative radiochemotherapy in patients with gastric cancer: one department's experience of 56 patients

56 pz trattati con 3DRT + CHT con 5FU

Follow-up mediano 17.4 mesi (range 3.5–47)

Sovrappvivenza media 15.4 mesi

Recidive locoregionali (RL) 7 (13%)

Metastasi a distanza (MD) 4 (7%)

RL+ MD 8 (14%)

Tossicità RTOG:

Tossicità ematologica: G3-4 10 pz (18%)

Tossicità gastrointestinale (diarrea) G3-4 19 pz (34%)



Caratteristiche dei pazienti

Nostra esperienza

75 pazienti dal 2007 al 2011

75 pazienti dal 2007 al 2011



Analizzati 60 pazienti con FU

Analizzati 67 pazienti con FU

| | No. pts (% of tot) |
|------------------------------|-----------------------|
| Mean age (years) | 64 |
| Range (years) | 82-34 |
| Range (years) | 82-34 |
| Gender | |
| - Male | 35 (58) |
| - Female | 25 (42) |
| T, stage | |
| - T1 | 6 (10) |
| | 25 (42) |
| | 18 (30) |
| | 11 (18) |
| - N0 | 5 (8) |
| - N1 | 31 (53) |
| - N2 | 12 (20) |
| - N3 | 11 (19) |
| Lauren classification | |
| | 29 (48) |
| - Diffuse type | 22 (37) |
| - Mixed type | 3 (5) |
| - Undifferentiated | 6 (10) |
| Tumor grade | |
| - 1 | 2 (3) |
| - 2 | 9 (15) |
| - 3 | 39 (65) |
| - 4 | 7 (12) |
| | 3 (5) |
| - Close/positive | 4 (7) |
| Stage ajcc 2002 | |
| - IB | 8 (14) |
| - IB | 8 (14) |
| - II | 18 (30) |
| - IIIA | 9 (16) |
| - IIIB | 5 (8) |
| Surgery | |
| Surgery | 25 (42) |
| - Total gastrectomy | 25 (42) |
| - Subtotal gastrectomy | 35 (59) |
| Chemotherapy regimen | |
| - 5-FU | 35 (58) |
| - Capecitabine | 23 (39) |



Risultati: recidive di malattia

Recidive Loco-regionali 5 pz:

2 pz in sede epigastrica

2 pz in sede epigastrica

3 pz a livello dei linfonodi loco-regionali

| <i>Relapse</i> | No. | % |
|----------------|-----|----|
| - Yes | | |
| - No | 55 | 92 |
| - No | 40 | 66 |
| - Liver | | 12 |
| - Bone | 2 | 3 |
| - Peritoneum | 2 | 3 |
| - Lung | 2 | 3 |
| - Diffuse | 6 | 10 |
| - Lymph nodes | 1 | 2 |



Risultati: Tossicità RTOG

| | <i>Grade 1</i> | | <i>Grade 2</i> | | <i>Grade 3</i> | | <i>Grade 4</i> | | <i>Total</i> | |
|------------------------------|----------------|----|----------------|----|----------------|---|----------------|----|--------------|----|
| | No. | % | No. | % | No. | % | No. | % | No. | % |
| <u>Acute Toxicity</u> | | | | | | | | | | |
| - Diarrhea | 4 | 7 | 5 | 2 | 3 | 0 | 0 | 9 | 15 | |
| - Dysphagia | 5 | 8 | 20 | 1 | 2 | 0 | 0 | 18 | 30 | |
| - Nausea/vomiting | 1 | 2 | 5 | 0 | 0 | 0 | 0 | 4 | 7 | |
| - Abdominal discomfort | | | | | | | | | | |
| Hematological | | | | | | | | | | |
| - WBC | 9 | 15 | | 17 | 2 | 3 | 0 | 0 | 21 | 35 |
| - Hgb | 3 | 5 | 4 | 7 | 1 | 2 | 0 | 0 | 8 | 14 |
| - PTL | 5 | 9 | 2 | 3 | 0 | 0 | 0 | 0 | 7 | 12 |
| <u>Late Toxicity</u> | | | | | | | | | | |
| | 2 | | 1 | 2 | | | 0 | 0 | 4 | 7 |
| | 1 | 2 | 0 | 0 | | 2 | 0 | 0 | 2 | 3 |
| | 1 | | 0 | 0 | | 0 | 0 | 0 | 1 | 2 |
| Hematological | | | | | | | | | | |
| - WBC | 0 | 0 | 2 | 3 | 0 | 0 | 0 | 0 | 2 | 3 |
| - Hgb | 2 | 3 | 1 | 2 | 0 | 0 | 0 | 0 | 3 | 5 |
| - PlgB | 0 | 0 | 2 | 3 | 0 | 0 | 0 | 0 | 2 | 3 |
| - PLT | 0 | 0 | 2 | 3 | 0 | 0 | 0 | 0 | 2 | 3 |

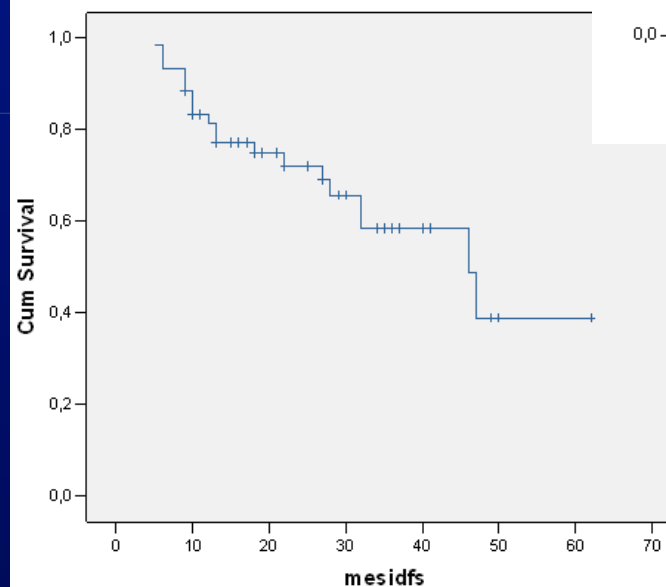
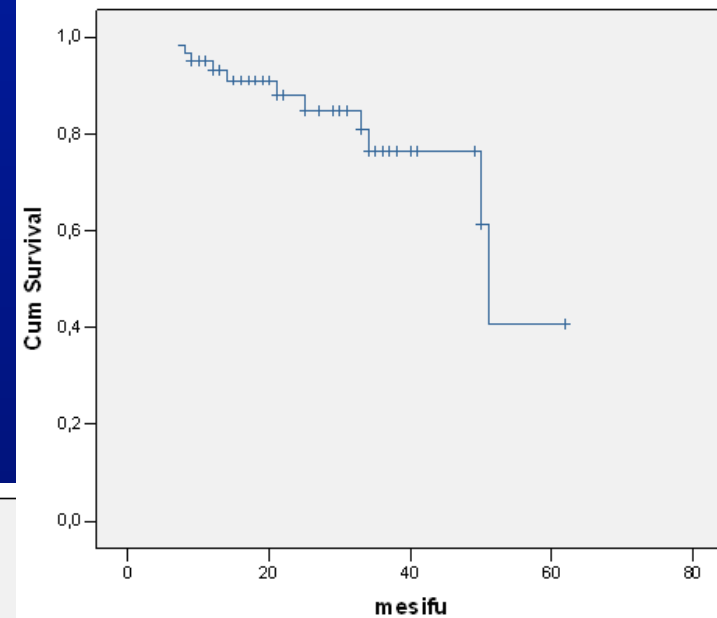


Risultati: Sopravvivenza

Impossibile visualizzare l'immagine. La memoria del computer potrebbe essere insufficiente per aprire l'immagine oppure l'immagine potrebbe essere danneggiata. Riavviare il computer e aprire di nuovo il file. Se viene visualizzata di nuovo la x rossa, potrebbe essere necessario eliminare l'immagine e inserirla di nuovo.

DFS:

- a 2 anni 77.3%
- a 5 anni 39%



OS:

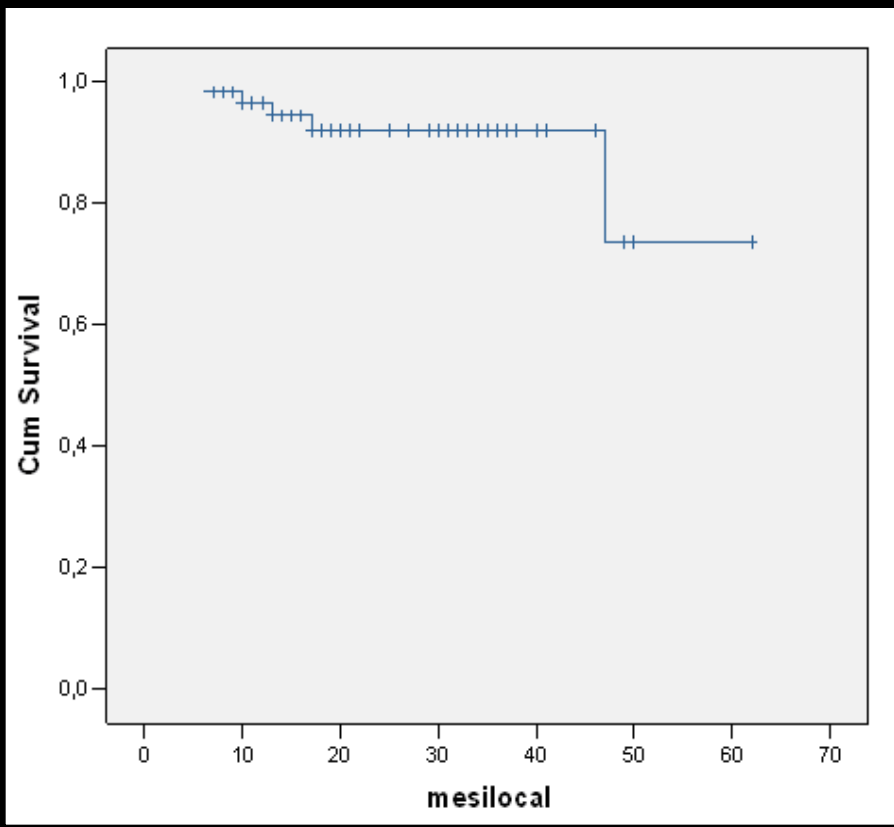
- a 2 anni 82%
- a 5 anni 32,5%

DSS:

- a 2 anni 91%
- a 5 anni 40.8%

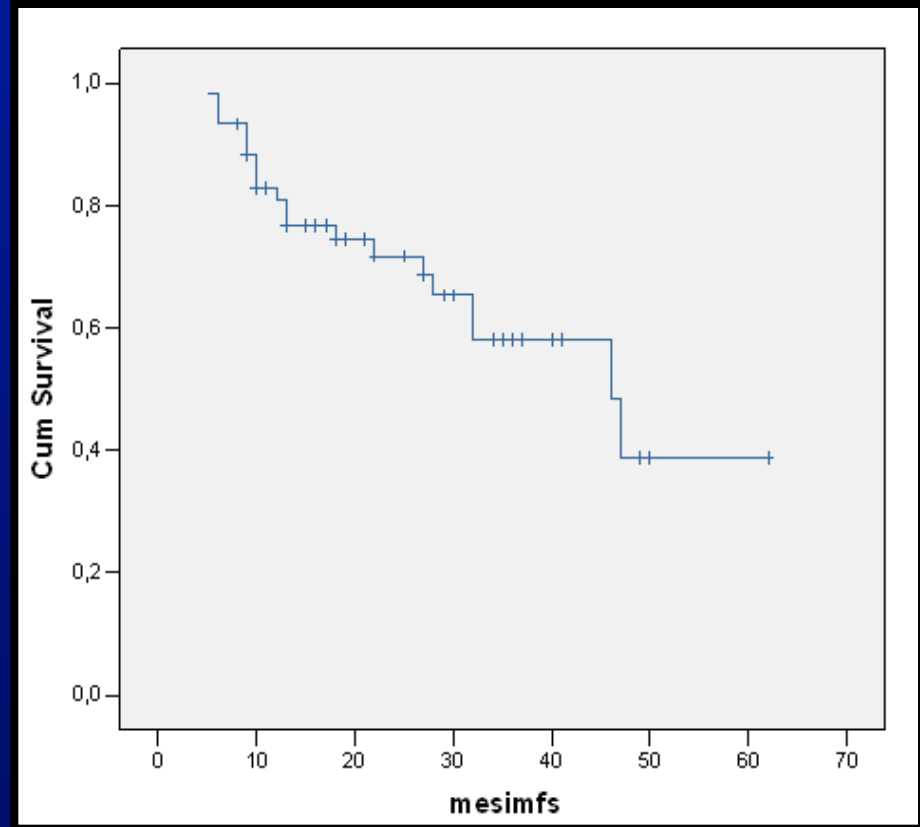


Risultati: Sopravvivenza



Controllo locale

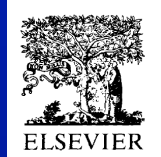
- a 2 anni 92%
- a 5 anni 73.6%



Metastasi a distanza

- a 2 anni 76%
- a 5 anni 38.7%

STUDIO DOSIMETRICO: 3D-CRT vs IMRT



IMRT for adjuvant radiation in gastric cancer: a preferred plan?

20 pazienti trattati con tecnica 3D-CRT, tra il 2000 ed il 2001

Per ogni paziente è stato ripetuto il piano con tecnica IMRT

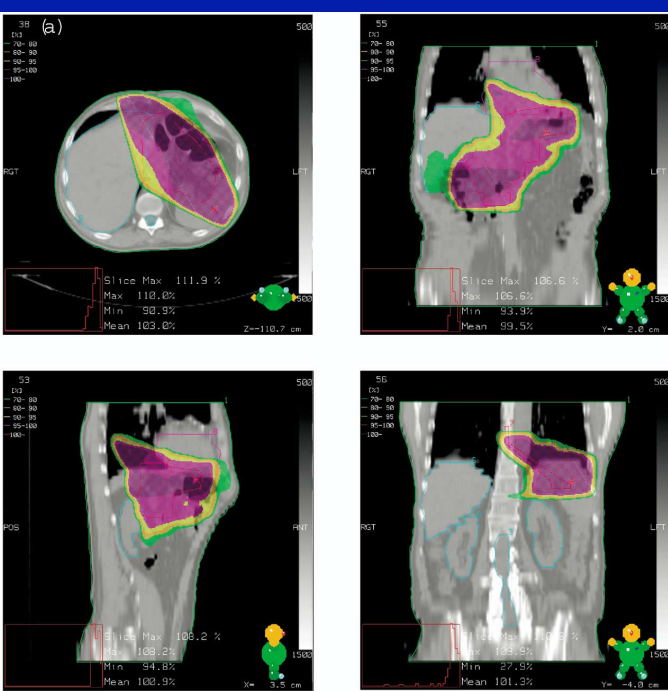
Sono stati confrontati in cieco da due radioterapisti i DVH dei due piani IMRT e 3D-CRT.

Table 2. Technical parameters of IMRT and conformal radiotherapy plans

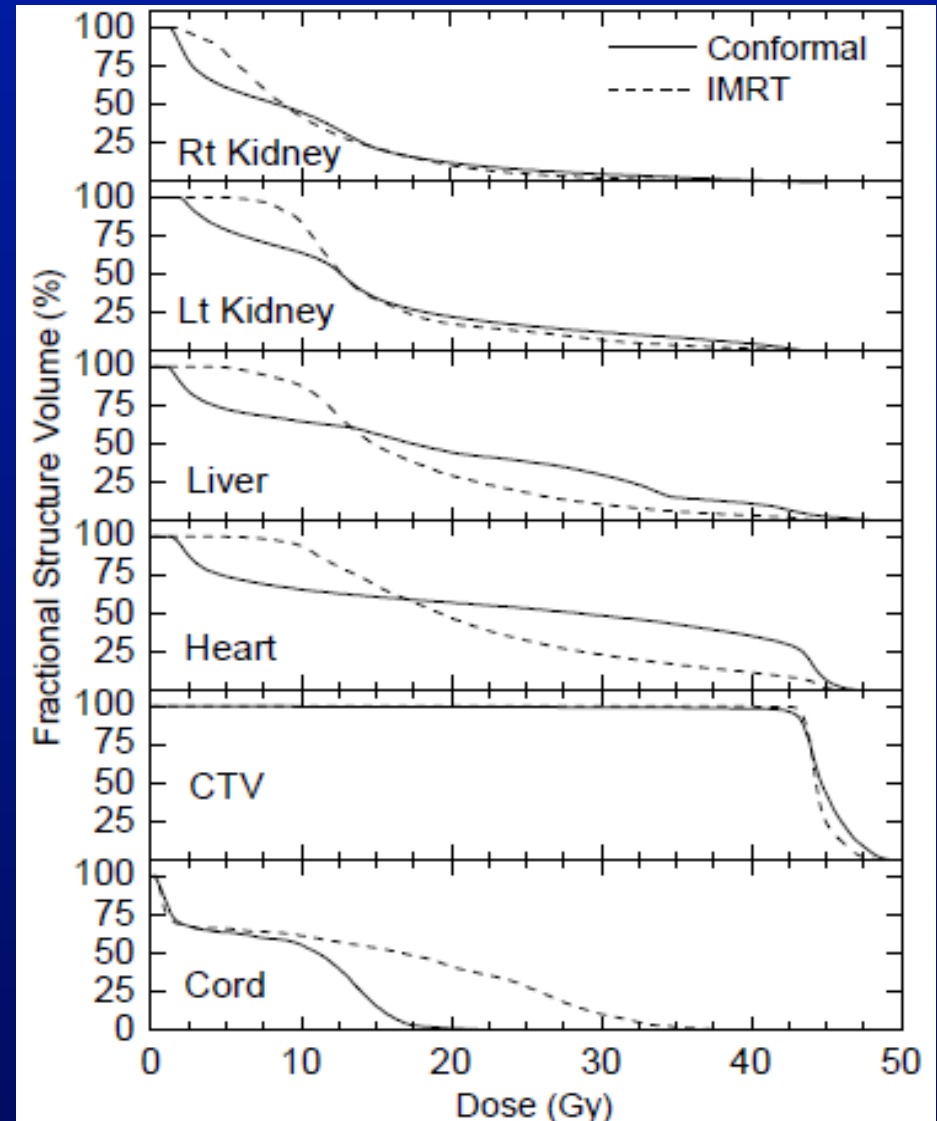
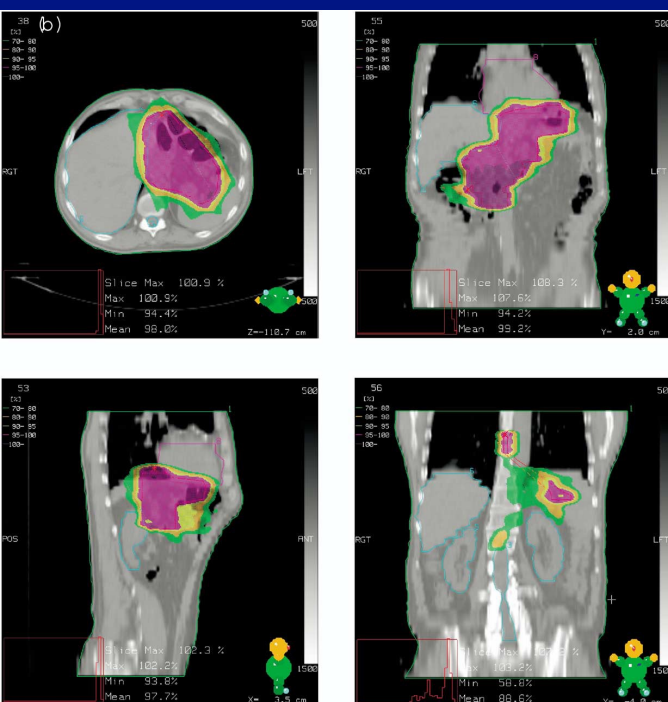
| Plan | Median of mean dose to PTV (Gy) (range) | UDV (cm ³) | Median D _{max} to spinal cord (Gy) | Left kidney (Gy) | | | Right kidney (Gy) | | | Liver (Gy) | | | Heart (Gy) | | |
|-----------|-----------------------------------------|------------------------|---------------------------------------------|------------------|-----------------|-----------------|-------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | | | | D ₈₀ | D ₅₀ | D ₂₀ | D ₈₀ | D ₅₀ | D ₂₀ | D ₈₀ | D ₅₀ | D ₂₀ | D ₈₀ | D ₅₀ | D ₂₀ |
| IMRT | 45.9 (44.4–47.1) | 1.7 | 36.85 | 11.84 | 15.50 | 26.50 | 7.84 | 12.75 | 20.00 | 11.75 | 17.29 | 30.40 | 2.75 | 12.89 | 32.65 |
| Conformal | 45.0 (42.9–46.4) | 4.1 | 45.65 | 11.50 | 16.06 | 36.10 | 3.20 | 12.75 | 26.00 | 3.40 | 27.97 | 43.00 | 2.50 | 15.50 | 42.10 |

DVH: 3D-CRT vs IMRT

3D-CRT



IMRT



In 18 su 20 pazienti è stato preferito il piano in IMRT poiché conferiva una maggiore copertura al target e un maggior risparmio OAR

In un caso non è stato scelto il piano IMRT per "hot spot" > 45 Gy a livello dell'intestino tenue e per dose al midollo spinale (circa 45 Gy)

In un caso uno dei due radioterapisti non ha scelto nessuno dei 2 piani, perciò è stato scelto un terzo revisore che ha preferito il piano IMRT

STUDIO SULL'OUTCOME 3D-CRT vs IMRT (1)

Combined adjuvant radiochemotherapy with imrt/xelox improves outcome with low renal toxicity in gastric cancer

Sono stati sottoposti a radioterapia adiuvante 60 pazienti affetti da carcinoma gastrico

| | 3D (<i>n</i> = 27) | IMRT (<i>n</i> = 33) |
|--------------|---------------------|-----------------------|
| | No. of patients (%) | No. of patients (%) |
| Chemotherapy | | |
| 5-FU/FA | 26 (96%) | 10 (30%) |
| XELOX | 1 (4%) | 23 (70%) |

Table 2. Summary of all radiation parameters

| | 3D-CRT (MV ± SD) | IMRT (MV ± SD) | <i>p</i> Value |
|-----------------------------------|---------------------|-------------------|----------------|
| N | 24 | 33 | |
| PTV (cm ³) | 1,397 ± 674 | 1,768 ± 625 | 0.0368 |
| V95% (cm ³) | 1,310 ± 635 | 1,501 ± 501 | NS |
| Left kidney, median (Gy) | 20.2 ± 10.0 | 16.8 ± 5.8 | NS |
| Left kidney, 30% (D30; Gy) | 26.8 ± 9.2 | 19.5 ± 5.5 | 0.0015 |
| Left kidney, 60% (D60; Gy) | 15.7 ± 9.3 | 14.3 ± 5.2 | NS |
| Right kidney, median (Gy) | 7.1 ± 5.1 | 13.7 ± 4.8 | <0.0001 |
| Right kidney, 30% (D30; Gy) | 11.6 ± 6.9 | 15.6 ± 4.3 | 0.0170 |
| Right kidney, 60% (D60; Gy) | 5.0 ± 3.4 | 11.8 ± 3.6 | <0.0001 |
| Spinal cord D _{max} (Gy) | 32.2 ± 8.6 | 38.7 ± 3.2 | 0.0016 |

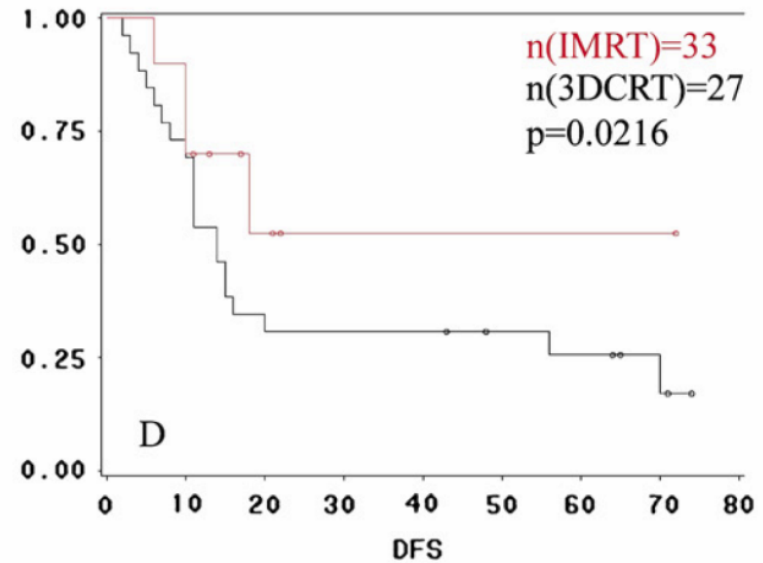
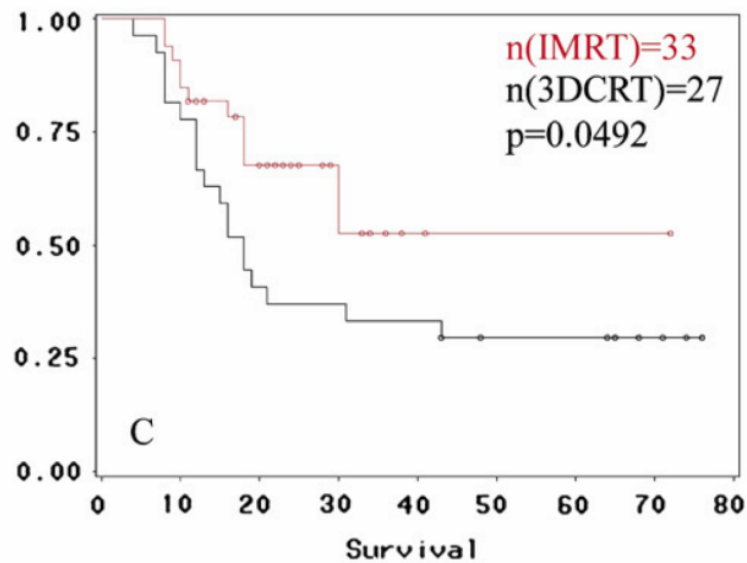


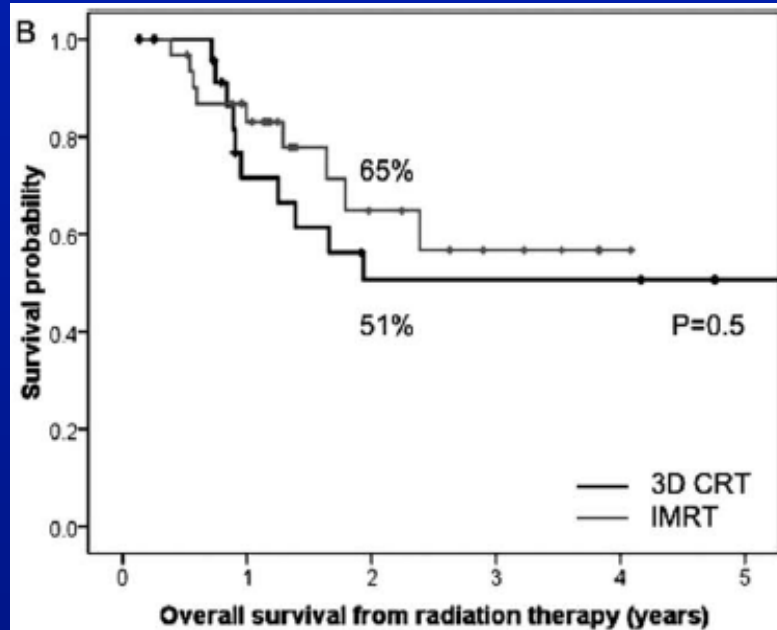
Table 3. Summary of renal toxicity based on creatinine levels

| | Creatinine ($\mu\text{mol/L}$, MV \pm SD) | | |
|-------------------------------------------------------|-----------------------------------------------|------------------|----------------|
| | 3D-CRT | IMRT | <i>p</i> Value |
| Before therapy | | | |
| ($n_{3\text{D-CRT}} = 25$, $n_{\text{IMRT}} = 30$) | 0.80 ± 0.17 | 0.74 ± 0.17 | NS |
| Maximum during therapy | | | |
| ($n_{3\text{D-CRT}} = 24$, $n_{\text{IMRT}} = 29$) | 0.81 ± 0.19 | 0.765 ± 0.18 | NS |
| Directly after therapy | | | |
| ($n_{3\text{D-CRT}} = 25$, $n_{\text{IMRT}} = 29$) | 0.78 ± 0.27 | 0.68 ± 0.20 | NS |
| 6 weeks after therapy | | | |
| ($n_{3\text{D-CRT}} = 25$, $n_{\text{IMRT}} = 29$) | 0.84 ± 0.21 | 0.71 ± 0.20 | 0.0210* |
| 1 year after therapy | | | |
| ($n_{3\text{D-CRT}} = 12$, $n_{\text{IMRT}} = 17$) | 0.88 ± 0.26 | 0.83 ± 0.20 | NS |
| Last available value [†] | | | |
| ($n_{3\text{D-CRT}} = 26$, $n_{\text{IMRT}} = 30$) | 1.19 ± 0.8 | 0.90 ± 0.35 | 0.0949* |

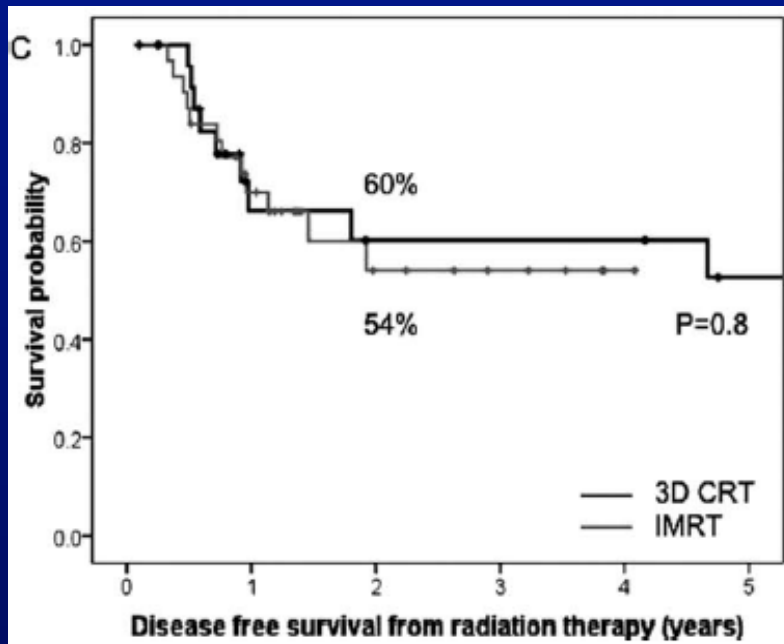
STUDIO SULL'OUTCOME 3D-CRT vs IMRT (2)

Comparison of Intensity-Modulated Radiotherapy and 3 Dimensional Conformal Radiotherapy as Adjuvant Therapy for Gastric Cancer

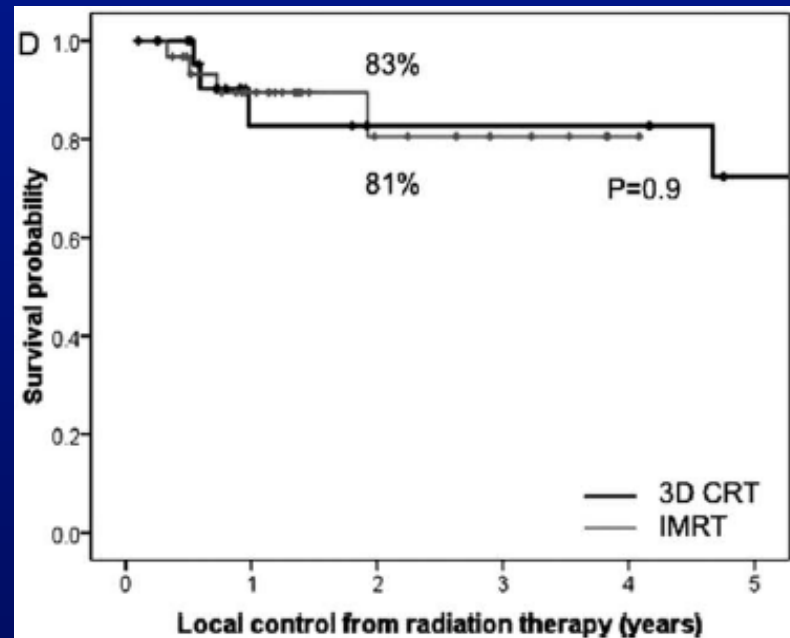
| | | 3D CRT (n=26) | IMRT (n=31) | P |
|------------------------------------|--------------------------------|------------------|------------------|------------------|
| Age at diagnosis, y | Median (range) | 58.6 (28.9-82.8) | 58.7 (38.0-76.4) | .74 |
| Gender | Man | 16 (61.5%) | 22 (71%) | .57 |
| | Woman | 10 (38.5%) | 9 (29.0%) | |
| Grade | Well differentiated | 0 (0%) | 3 (9.7%) | .50 |
| | Moderately differentiated | 6 (23.1%) | 2 (6.5%) | |
| | Poorly differentiated | 17 (65.4%) | 25 (80.6%) | |
| | Grade not assessed | 3 (11.5%) | 1 (3.2%) | |
| T classification | 1 | 2 (7.7%) | 1 (3.2%) | .43 |
| | 2a/b | 13 (50%) | 13 (42%) | |
| | 3 | 9 (34.6%) | 16 (51.6%) | |
| | 4 | 2 (7.7%) | 1 (3.2%) | |
| N classification | 0 | 5 (19.2%) | 3 (9.7%) | .55 |
| | 1 | 11 (42.3%) | 16 (51.6%) | |
| | 2 | 5 (19.2%) | 9 (29.0%) | |
| | 3 | 5 (19.2%) | 3 (9.7%) | |
| Surgery | Ivor-Lewis esophagogastrectomy | 6 (23.1%) | 8 (25.8%) | |
| | Total gastrectomy | 8 (30.8%) | 10 (32.3%) | |
| | Subtotal gastrectomy | 12 (46.2%) | 13 (41.9%) | |
| Location | GE junction | 5 (19.2%) | 9 (29.0%) | |
| | Cardia/proximal one-third | 1 (3.8%) | 3 (9.7%) | |
| | Body/middle one-third | 5 (19.2%) | 3 (9.7%) | |
| | Antrum/distal one-third | 14 (53.8%) | 13 (41.9%) | |
| | Diffuse | 1 (3.8%) | 3 (9.7%) | |
| Surgical margins | Negative | 20 (76.9%) | 18 (58.1%) | .17 |
| | Close (<3 mm) | 0 (0%) | 7 (22.6%) | |
| | Positive | 6 (23.1%) | 6 (19.3%) | |
| No. of lymph nodes dissected | Median (range) | 20 (4-56) | 19 (1-49) | |
| No. of lymph nodes positive | Total (range) | 5 (0-27) | 5 (0-20) | 1.0 |
| | % Positive (range) | 32.3% (0-100%) | 28.6% (0-88.2%) | .79 |
| Total dose, Gy | Median (range) | 45 (43.2-50.4) | 45 (41.4-54) | .01 ^a |
| Concurrent chemotherapy | 5-FU | 20 (77%) | 5 (16%) | |
| | Capecitabine | 5 (19%) | 26 (84%) | |
| | None | 1 (4%) | 0 (0%) | |
| Pre-RT and/or post-RT chemotherapy | 5-FU | 2 (7.7%) | 2 (6.45%) | .74 |
| | Carboplatin/5-FU | 17 (65.4%) | 6 (19.4%) | |
| | Carboplatin/capecitabine | 5 (19.2%) | 19 (61.3%) | |
| | Capecitabine | 0 (0%) | 2 (6.45%) | |
| | EOX | 0 (0%) | 1 (3.2%) | |
| | None | 2 (7.7%) | 1 (3.2%) | |



OS a 2 anni



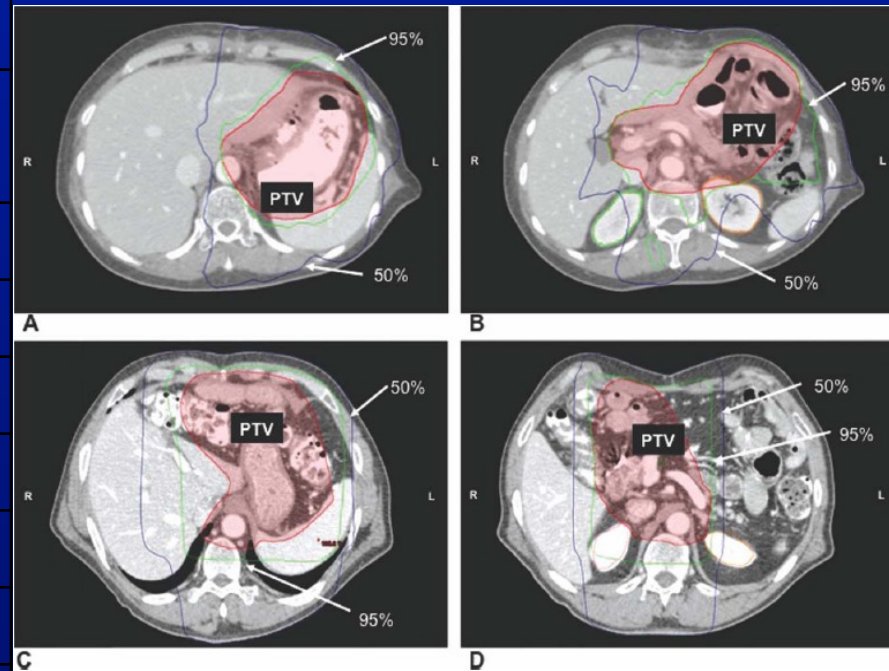
DFS a 2 anni



Controllo locale

Parametri DVH

| | 3D-CRT | IMRT | P |
|-------------------|-----------|-----------|------------------|
| | Median | Median | P |
| Both kidneys, cGy | 1109 | 1388 | 0,5 |
| V20% | 22 | 18 | 0,18 |
| Right kidney, cGy | 1036 | 1197 | 0,04 |
| V20% | 15 | 13 | 0,55 |
| Left kidney, cGy | 1205 | 1528,5 | 0,06 |
| V20% | 32 | 22,2 | 0,31 |
| Liver, cGy | 1860 | 1725 | 0,19 |
| V30% | 28 | 16 | <0,001 |



(A e B) IMRT; (C e D) 3D-CRT.
Le linee di isodose 50% e 95% mostrano un risparmio del fegato e del rene nel piano IMRT

Tossicità acuta 3D-CRT vs IMRT

Table 2. Acute Gastrointestinal Toxicity^a

| | | Grade | | | Total Grade ≥2 |
|----------|-------------------|----------|---------|--------|----------------|
| | | 2 | 3 | 4-5 | |
| Nausea | 3D CRT | 10 (39%) | 4 (15%) | 0 (0%) | 14 (54%) |
| | IMRT ^b | 11 (36%) | 4 (13) | 0 (0%) | 15 (49%) |
| Vomiting | 3D CRT | 4 (15%) | 0 (0%) | 0 (0%) | 4 (15%) |
| | IMRT ^b | 1 (3%) | 0 (0%) | 0 (0%) | 1 (3%) |
| Anorexia | 3D CRT | 8 (31%) | 3 (12%) | 0 (0%) | 11 (43%) |
| | IMRT ^b | 8 (26%) | 5 (16%) | 0 (0%) | 13 (42%) |
| Diarrhea | 3D CRT | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | IMRT ^b | 2 (7%) | 0 (0%) | 0 (0%) | 2 (7%) |

3D CRT indicates 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

^aToxicities were scored using the Common Terminology Criteria for Adverse Events (version 3.0).

^bInformation was unavailable for 3 patients.

STUDIO DOSIMETRICO: 3D-CRT, AP/PA, IMRT, TOMOTHERAPY

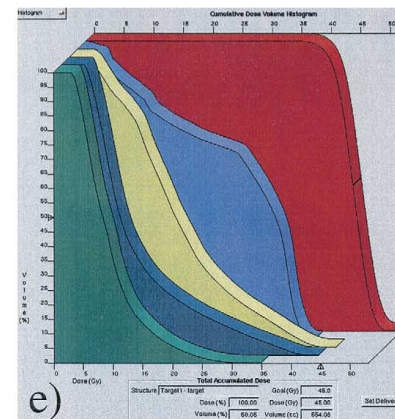
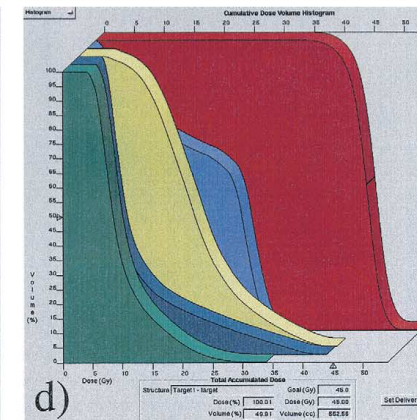
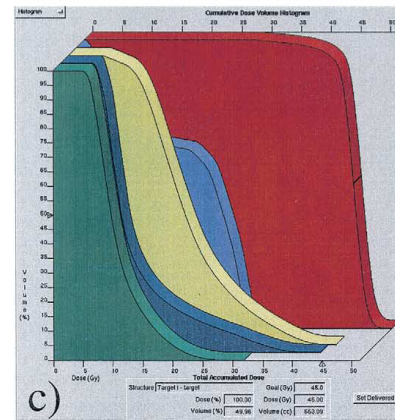
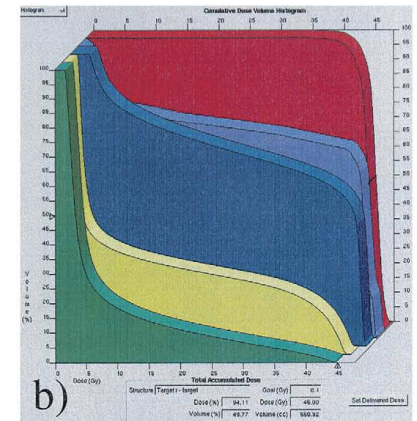
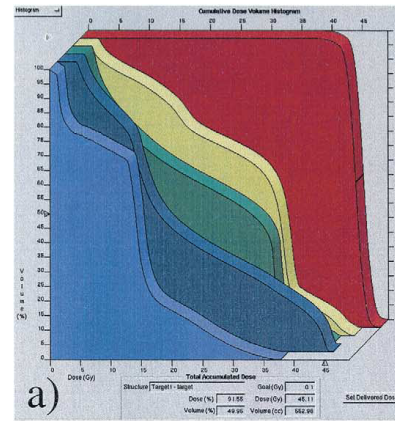
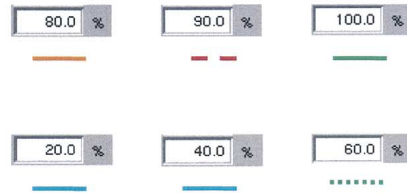
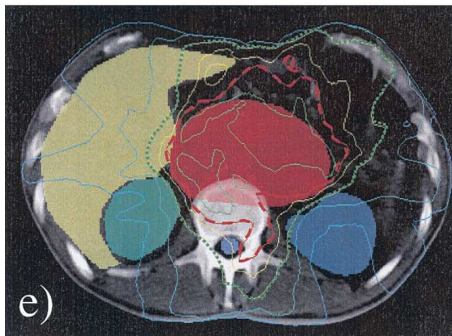
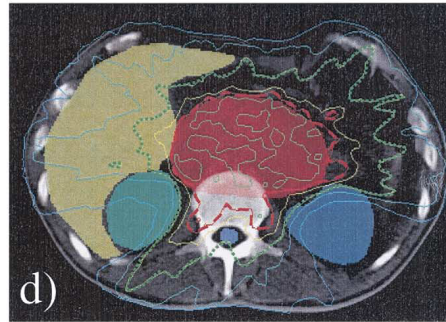
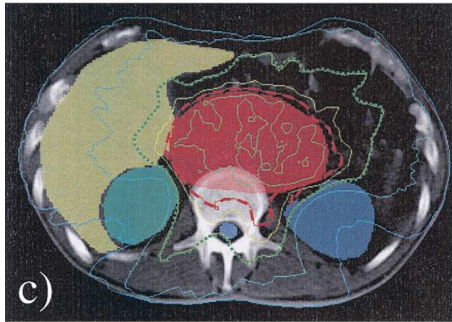
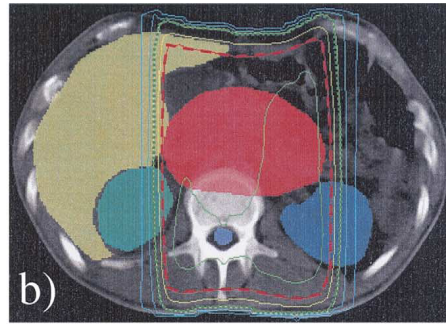
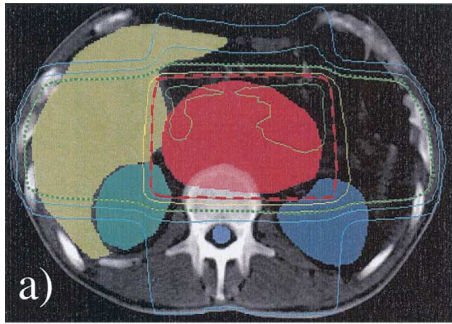


IMRT for postoperative treatment of gastric cancer: covering large target volumes in the upper abdomen: a comparison of a step-and-shoot and an arc therapy approach.

Sono stati selezionati 15 pazienti trattati con 3D-CRT.

Per ogni paziente sono stati creati 5 piani:

- 3D-CRT
- AP-PA
- Step-and-shoot IMRT
- Tomotherapy con collimazione di 1 cm
- Tomotherapy con collimazione di 2 cm



- Target
- Spinal Cord
- Liver
- L. Kidney
- R. Kidney

a) 3D-CRT
 b) AP-PA
 c) Tomotherapy con collimazione di 1 cm
 d) Tomotherapy con collimazione di 2 cm
 e) Step-and-shoot IMRT

Risultati

Table 3. Clinically relevant plan parameters for the different treatment approaches*

| | Conventional conformal 3D plan | Conventional AP-PA plan | 8-field step-and- shoot intensity- modulated radiotherapy | Tomotherapy (1-cm collimation) | Tomotherapy (2-cm collimation) |
|------------------------------------------------------------------|-----------------------------------|----------------------------|--------------------------------------------------------------------|-----------------------------------|-----------------------------------|
| Prescription dose = median dose to target (at % of maximum dose) | 45 Gy (94.3%) | 45 Gy (93.5%) | 45 Gy (84.1%) | 45 Gy (86.6%) | 45 Gy (83.7%) |
| Maximum dose (at % of prescription dose) | 47.70 Gy (105.8%) | 48 Gy (107.0%) | 53.5 Gy (119.1%) | 52.0 Gy (115.6%) | 53.8 Gy (119.7%) |
| Volume exposed to more than 110% of prescription dose | 0% | 0% | 2.54% | 0.33% | 1.41% |
| Dose delivered to >90% (95%) of target | 43.4 Gy (42.6 Gy) | 44.0 Gy (43.4 Gy) | 41.9 Gy (40.9 Gy) | 42.8 Gy (41.2 Gy) | 42.2 Gy (41.0 Gy) |
| Dose to left kidney (\pm standard deviation) | | | | | |
| Median dose | 19.5 Gy (\pm 7.6) | 31.2 Gy (\pm 17.6) | 9.5 Gy (\pm 1.8) | 9.7 Gy (\pm 0.4) | 8.1 Gy (\pm 0.4) |
| Dose exceeded by 30% of volume | 26.2 Gy (\pm 5.6) | 39.0 Gy (\pm 14.1) | 12.7 Gy (\pm 2.0) | 12.0 Gy (\pm 0.5) | 10.2 Gy (\pm 0.3) |
| Dose exceeded by 60% of volume | 16.3 Gy (\pm 8.4) | 25.9 Gy (\pm 17.4) | 8.6 Gy (\pm 1.6) | 9.0 Gy (\pm 0.4) | 7.5 Gy (\pm 0.4) |
| NTCP left kidney | | | | | |
| (TD 5/5 = 23 Gy, TD 50/5 = 28 Gy) | 31.3% (\pm 35.9) | 69.3% (\pm 42.0) | 0.3% (\pm 0.3) | 0.2% (\pm 0.1) | 0.1% (\pm 0.1) |
| (TD 5/5 = 15 Gy, TD 50/5 = 20 Gy) | 82.6% (\pm 23.5) | 87.0% (\pm 27.8) | 22.7% (\pm 13.9) | 17.7% (\pm 8.1) | 9.9% (\pm 4.8) |
| Dose to right kidney (\pm standard deviation) | | | | | |
| Median dose | 8.3 Gy (\pm 6.3) | 4.7 Gy (\pm 4.8) | 7.4 Gy (\pm 1.6) | 8.6 Gy (\pm 1.8) | 7.1 Gy (\pm 1.5) |
| Dose exceeded by 30% of volume | 14.4 Gy (\pm 8.5) | 9.5 Gy (\pm 9.6) | 9.9 Gy (\pm 2.0) | 10.8 Gy (\pm 1.7) | 9.0 Gy (\pm 1.7) |
| Dose exceeded by 60% of volume | 6.0 Gy (\pm 4.3) | 3.8 Gy (\pm 3.5) | 6.5 Gy (\pm 1.5) | 7.8 Gy (\pm 1.8) | 6.5 Gy (\pm 1.5) |
| NTCP right kidney | | | | | |
| (TD 5/5 = 23 Gy, TD 50/5 = 28 Gy) | 2.2% (\pm 7.8) | 3.3% (\pm 11.8) | 0.0% (\pm 0.0) | 0.0% (\pm 0.0) | 0.0% (\pm 0.0) |
| (TD 5/5 = 15 Gy, TD 50/5 = 20 Gy) | 19.3% (\pm 29.0) | 18.1% (\pm 31.4) | 1.8% (\pm 1.8) | 2.0% (\pm 2.2) | 1.4% (\pm 2.2) |
| Dose to liver (excluding target \pm standard deviation) | | | | | |
| Median dose | 23.4 Gy (\pm 5.0) | 3.7 Gy (\pm 2.8) | 17.9 Gy (\pm 1.6) | 17.9 Gy (\pm 1.1) | 18.1 Gy (\pm 0.7) |
| Dose exceeded by 30% of volume | 26.4 Gy (\pm 5.2) | 16.4 Gy (\pm 14.1) | 22.3 Gy (\pm 1.6) | 21.7 Gy (\pm 1.3) | 21.8 Gy (\pm 0.8) |
| Dose exceeded by 60% of volume | 21.1 Gy (\pm 4.6) | 2.8 Gy (\pm 1.2) | 16.0 Gy (\pm 1.9) | 16.5 Gy (\pm 1.1) | 16.7 Gy (\pm 0.7) |
| NTCP liver | | | | | |
| (TD 5/5 = 23 Gy, TD 50/5 = 28 Gy) | 2.5% (\pm 2.2) | 0.5% (\pm 0.9) | 1.2% (\pm 0.6) | 1.2% (\pm 0.3) | 1.3% (\pm 0.6) |
| Maximum dose to spinal cord (\pm standard deviation) | 30.5 Gy (\pm 7.5) | 47.3 Gy (\pm 0.9) | 39.9 Gy (\pm 1.2) | 30.7 Gy (\pm 2.8) | 31.4 Gy (\pm 4.4) |
| Segments (step-and-shoot) and arcs (tomotherapy) used | 3-4 | 2 | 49 (range, 37-77) | 11 (range, 9-12) | 6 (range, 5-6) |

STUDIO SULL'OUTCOME: IMRT

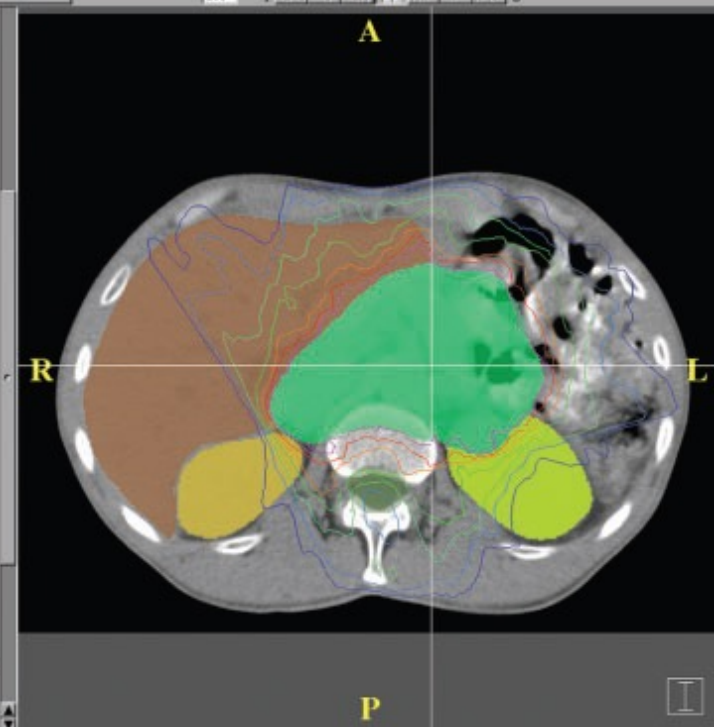
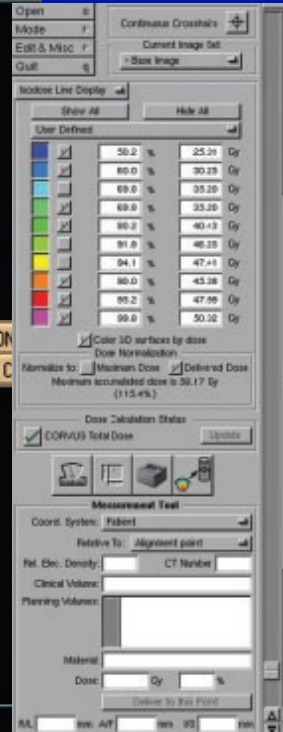
Intensity-modulated radiation therapy in the treatment of gastric cancer: early clinical outcome and dosimetric comparison with conventional techniques

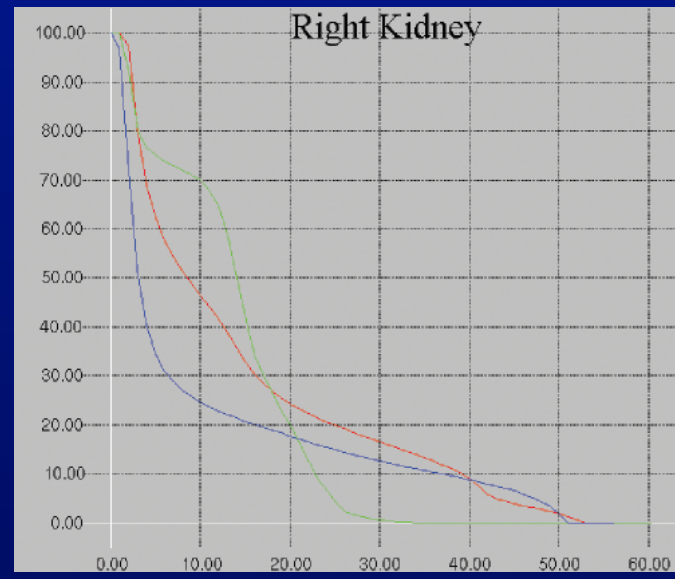
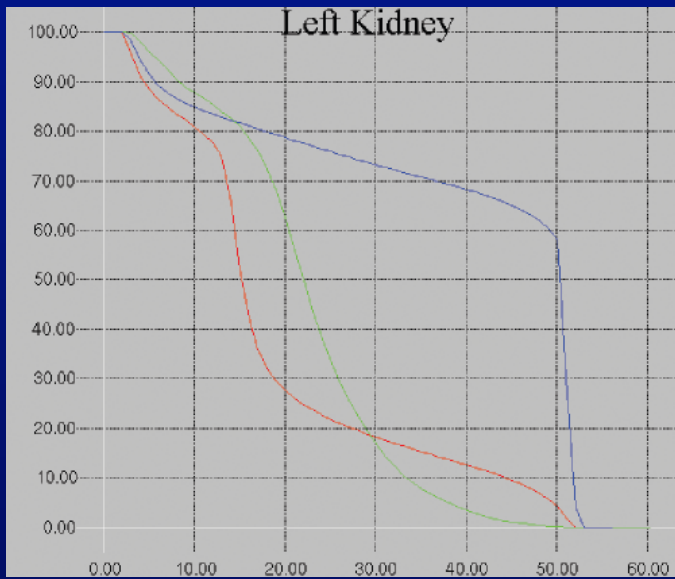
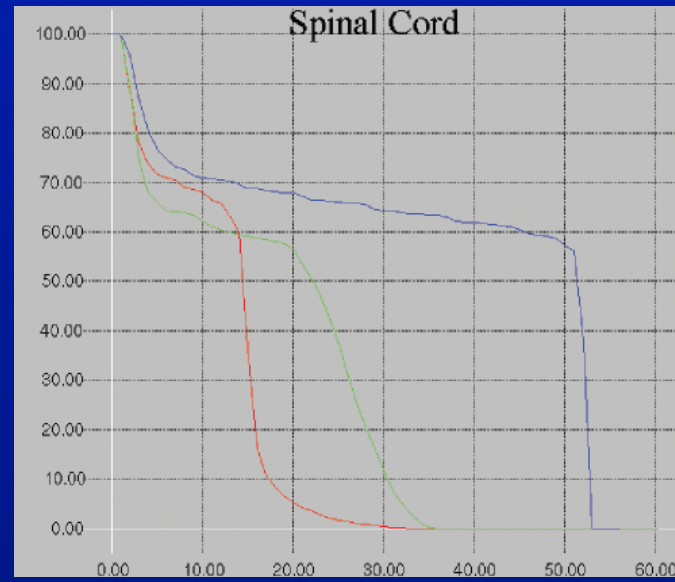
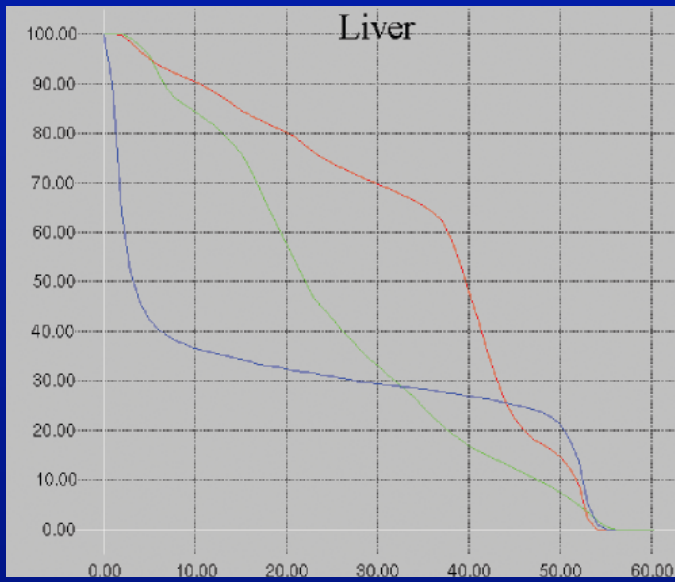
7 trattati con IMRT

- 6 pz in associazione con 5-FU e leucovorina → Dose 50,4 Gy in 1,8 Gy
- 1 pz RT esclusiva → Dose 45 Gy in 1,8 Gy + 5,4 Gy di boost

IMRT comparata con AP/PA e 3campi (AP/PA+ campo laterale sinistro).

Curve di isodose in sezione assiale





ROSSO: AP/PA; BLU: 3 fields; VERDE: IMRT

RISULTATI IN TERMINI DOSIMETRICI:

Mean dose to structures (percentage of prescribed dose)

| Structure | 2F | 3F | IMRT | p-values* | | |
|--------------|--------------|--------------|--------------|------------------|-------------------|----------|
| | | | | 3F vs IMRT | 2F vs IMRT | 2F vs 3F |
| PTV | 102.0 ± 0.7% | 100.5 ± 1.8% | 105.7 ± 1.3% | NS | 0.0014 | 0.044 |
| Right kidney | 24.8 ± 14.9% | 28.7 ± 13.0% | 18.9 ± 9.8% | 0.022 | NS | NS |
| Left kidney | 62.7 ± 38.2% | 67.9 ± 38.2% | 58.4 ± 19.1% | NS | 0.0049 | NS |
| Liver | 41.6 ± 9.5% | 62.9 ± 17.8% | 44.6 ± 6.8% | 0.018 | NS | 0.0055 |

Volume of structures receiving greater than the threshold dose for 50.4 Gy treatment

| Structure | Dose (Gy) | Volume above given dose (%) | | | p-values* | | |
|-----------|-----------|-----------------------------|------------|------------|------------|------------|----------|
| | | 2F | 3F | IMRT | 3F vs IMRT | 2F vs IMRT | 2F vs 3F |
| PTV | 55.4 | 1.3 ± 2.4 | 0.7 ± 1.6 | 4.4 ± 3.9 | NS | NS | NS |
| PTV | 50.4 | 84.1 ± 11.1 | 94.9 ± 4.0 | 98.1 ± 1.2 | NS | 0.016 | 0.022 |

(b) Organs at Risk

| | | | | | | | |
|--------------|------|-------------|-------------|-------------|-------|---------|---------|
| Right kidney | 20.0 | 20.1 ± 18.0 | 20.9 ± 16.6 | 11.6 ± 8.3 | 0.027 | NS | NS |
| Left kidney | 20.0 | 67.6 ± 34.7 | 52.0 ± 31.9 | 52.1 ± 28.9 | NS | NS | NS |
| Liver | 30.0 | 33.7 ± 12.6 | 63.6 ± 28.5 | 18.9 ± 12.9 | 0.010 | 0.030 | 0.0062 |
| Spinal cord | 45.0 | 55.0 ± 22.3 | 4.1 ± 7.3 | 0 | NS | 0.00039 | 0.00033 |

RISULTATI IN TERMINI DI TOLLERANZA:

Per quanto riguarda la tolleranza: nessun pz ha sviluppato una tossicità gastrointestinale ed ematologica superiore a G2

| Grade | 0 | 1 | 2 | >2 |
|-----------------|---|---|---|----|
| Upper GI | 0 | 0 | 7 | 0 |
| Lower GI | 3 | 1 | 3 | 0 |
| Oesophagitis | 4 | 1 | 2 | 0 |
| Haematological* | 2 | 2 | 3 | 0 |

Tossicità della cute era grado 0-1 in tutti i pazienti.

Non sono state rilevate anomalie di laboratorio per quanto concerne la funzionalità renale (rispetto ai valori pre-trattamento)

Nessun pz ha interrotto il trattamento

STUDIO DOSIMETRICO: TOMOTERAPY vs 3D-CRT, IMRT

Adjuvant radiotherapy for gastric cancer: a dosimetric comparison of 3-dimensional conformal radiotherapy, tomotherapy and conventional intensity modulated radiotherapy treatment plans

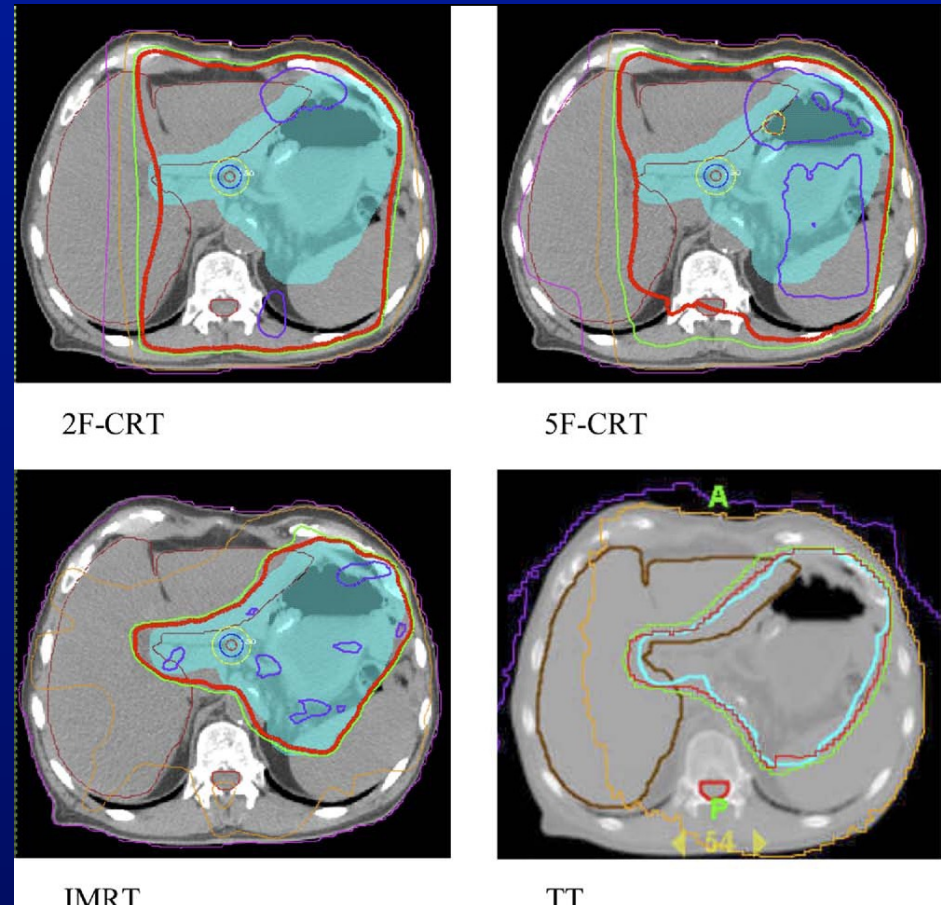
Sono stati creati 4 piani di trattamento radioterapico per 5 pazienti con carcinoma gastrico precedentemente trattati con radio-chemioterapia adiuvante

3D-CRT a 2 campi (2F)

3D-CRT a 5 campi (5F)

IMRT

Tomoterapia



PTV coverage and homogeneity

Table 1. The percentage of the PTV receiving more or less than the prescribed dose of 4500cGy (median, range)

| Technique | <90% | <95% | >105% | >110% | >115% |
|-----------|---------------|---------------|--------------------|---------------|---------------|
| TT | 0.4 (0–1.8) | 1.5 (0.7–3.5) | 0.3 (0.1–2) | 0 | 0 |
| 2F-CRT | 0 (0–0.2) | 0.1 (0.1–0.9) | 53.9 (11.5–67.7) | 6.5 (0–22.9) | 0 (0–1.8) |
| 5F-CRT | 0.1 (0–0.1) | 0.7 (0–3) | 65.7 (40.1–75.9) | 4.7 (0–34.1) | 0 (0–0.4) |
| IMRT | 0.3 (0.1–1.1) | 1.2 (0.8–2.8) | → 69.6 (63.3–83.2) | 28.9 (2.2–44) | → 3.8 (0–5.1) |

Table 4. The mean and maximum doses (Gy) in the PTV (median, range)

| Technique | Mean Dose | Maximum Point Dose | Maximum Dose to 1.5cm ² Area |
|-----------|------------------|--------------------|-----------------------------------------|
| TT | 45.8 (45.4–46.3) | 48 (47–48.5) | 47.4 (47.2–47.9) |
| 2F-CRT | 47.7 (46.4–48.3) | 51.6 (49.3–53.2) | 52.3 (49–52.9) |
| 5F-CRT | 48 (47–48.5) | 50.9 (50.2–53.1) | 50.5 (50–52.2) |
| IMRT | 48.3 (47.7–49.2) | 56.31 (52.5–60.7) | 55 (51–57) |

OAR Dosimetry

Table 2. Median values for dose received by the left (L) and right (R) kidneys (K)

| Parameter | TomoTherapy® | 2F-CRT | 5F-CRT | IMRT |
|--------------|-------------------------|------------------|------------------|-------------------------|
| LK V5 | 100 (88.6–100) | 72.3 (59.7–89.8) | 90.2 (72.2–99.3) | 98.3 (94–100) |
| LK V20 | <u>27.9 (11.4–31.5)</u> | 56.7 (34.7–65.2) | 50.8 (22.1–75.1) | <u>26.8 (12.5–30.3)</u> |
| LK mean dose | 17.6 (14.9–19.4) | 27.2 (17.8–32.7) | 24.6 (14.5–34.5) | 16.7 (11.3–19.8) |
| LK D80 | 11.5 (6.1–13.9) | 4.3 (3.6–7.1) | 10.3 (4.4–16.7) | 10.7 (5.7–11.1) |
| LK D50 | <u>14.5 (9.2–16.8)</u> | 29.5 (6.6–43.3) | 20.6 (9.7–41.8) | <u>13.8 (7.4–15.2)</u> |
| LK D20 | <u>23.2 (18–32.5)</u> | 47.4 (42.7–50.9) | 43.9 (21.9–48.3) | <u>25.4 (14.3–30.5)</u> |
| RK V5 | 96.7 (80.5–100) | 65.1 (38.8–92) | 89 (63.5–98.6) | 94.3 (79.1–100) |
| RK V20 | <u>13.6 (7.9–28.8)</u> | 50.6 (21–69.8) | 59.6 (20.4–65.4) | <u>18.7 (14.5–24.4)</u> |
| RK mean dose | 14.3 (12–16.6) | 24.7 (11.7–32.1) | 25.9 (13–29.7) | 14.6 (9.8–18.4) |
| RK D80 | 10.4 (5.1–11.5) | 3 (2.5–11.8) | 8.9 (3.6–14.4) | 7.1 (5–13.7) |
| RK D50 | <u>13.2 (9.7–15.4)</u> | 21.5 (3.8–38) | 25.1 (8.9–33.2) | <u>12.9 (6.7–16.3)</u> |
| RK D20 | <u>18.4 (16.2–24.2)</u> | 46.5 (21.7–48.8) | 42 (20.4–48.3) | <u>19.7 (15.7–21.5)</u> |

Table 3. Median values for dose received by the liver

| Parameter | TomoTherapy® | 2F-CRT | 5F-CRT | IMRT |
|-----------|-----------------------|------------------|------------------|-------------------------|
| V5 | 100 (99.3–100) | 67.7 (48.4–73.6) | 82.7 (73.3–85.6) | 100 (98.6–100) |
| V30 | <u>37 (22.1–43.6)</u> | 45 (33.1–52.6) | 61.6 (45–67.3) | <u>34.7 (19.4–41.8)</u> |
| Mean dose | 27.1 (21.9–29.7) | 23.9 (18.4–27.5) | 31 (24.5–32.6) | 27.3 (23.4–30.4) |
| D80 | 15.7 (11.4–20.4) | 3.3 (2.2–3.8) | 6.3 (3.9–9.1) | 17.3 (15.2–21.2) |
| D50 | 23.9 (19–28.1) | 19.3 (4.6–35.6) | 38.4 (23.4–39.8) | 25 (22.4–27.9) |
| D20 | 41.1 (31.6–43.3) | 46.5 (45.9–46.9) | 47.5 (45.5–47.9) | 38.5 (29.8–43) |

| | | | | |
|------------------------------------------|--------------------------|---------------------|---------------------|--------------------------|
| Median maximum point dose to spinal cord | <u>26.8 (10.8–39) Gy</u> | 48.5 (47.7–49.6) Gy | 48.9 (47.8–49.7) Gy | <u>25.8 (19.8–37) Gy</u> |
|------------------------------------------|--------------------------|---------------------|---------------------|--------------------------|

IORT



La IORT aumenta efficacia associazione chirurgia e radioterapia

Consente eradicazione eventuale residuo tumorale subclinico;

Sfrutta l'effetto radiobiologico della dose singola e ottiene livelli di dose totale superiori alla sola irradiazione esterna

Potenzia combinazione terapeutica, la precocità dell'irradiazione può evitare la ricrescita tumorale nell'intervallo fra l'intervento e la successiva radioterapia postoperatoria

**LONG-TERM RESULTS AFTER INTRAOPERATIVE RADIATION
THERAPY FOR GASTRIC CANCER**

OLIVER DROGNITZ, M.D., PH.D.,* KARL HENNE, M.D.,† CHRISTIAN WEISSENBERGER, M.D., PH.D.,†
GREGOR BRUGGMOSER, M.D., PH.D.,† HEIKE GÖBEL, M.D.,‡ ÜLRICH THEODOR HOPT, M.D., PH.D.,*
HERRMANN FROMMHOLD, M.D., PH.D.,† AND GÜNTHER RUF, M.D., PH.D.*

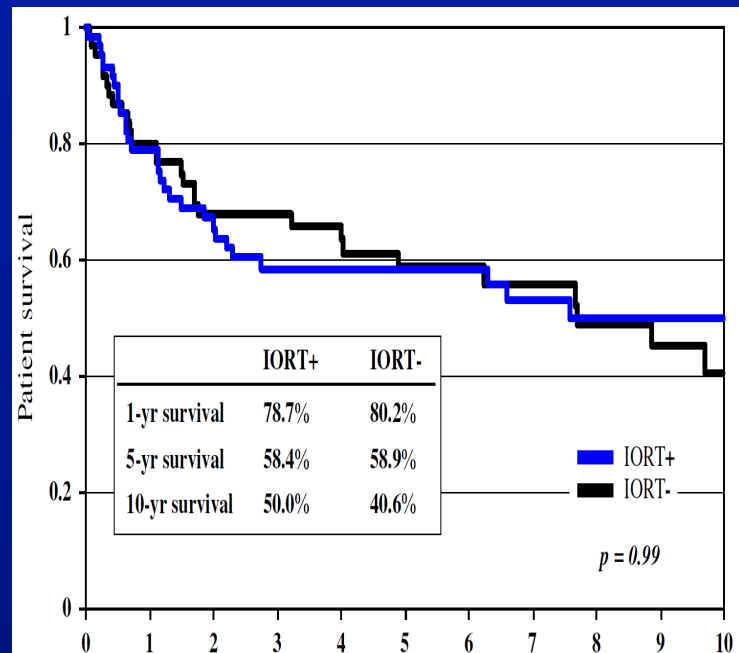
**Dal 1991 al 2001, 84 pazienti sono stati sottoposti a chirurgia + IORT
(23 Gy, 6-15 MeV) (IORT+)**

**I pazienti con una storia di chemioterapia neoadiuvante, R1 o R2, o
sottoposti a re-intervento dopo recidiva locale sono stati esclusi da
ulteriori analisi.**

**I rimanenti 61 pazienti sono stati retrospettivamente confrontati con 61
pazienti IORT-**

Table 2. Surgical complications and long-term tumor control

| Category | IORT ⁺ (n = 61) | IORT ⁻ (n = 61) | p |
|------------------------------------|-------------------------------|-------------------------------|-------|
| Perioperative mortality | 3 (4.9%) | 3 (4.9%) | NS |
| Total surgical morbidity | 27 (44.3%) | 12 (19.7%) | <0.05 |
| Anastomotic leakage | 10 (16.3%) | 5 (8.2%) | 0.27 |
| Abdominal or intestinal hemorrhage | 5 (8.2%) | 2 (3.3%) | NS |
| Abdominal abscess | 6 (9.8%) | 4 (6.6%) | NS |
| Pancreatitis | 5 (8.2%) | 0 (0) | 0.057 |
| Small-bowel obstruction | 1 (1.6%) | 1 (1.6%) | NS |
| Long-term tumor control | | | |
| Locoregional tumor recurrence | 6 (9.8%) | * | |
| Peritoneal metastasis | 19 (31.1%) | * | |
| Distant metastasis | 12 (19.7%) | * | |



Non c'è differenza
significativa tra OS tra IORT
+ e IORT-

(p = 0.99)

Le complicanze chirurgiche sono più comuni nel
gruppo IORT+ (p < 0,05)

IORT associata a un più basso tasso di recidiva
(19.8%) ma non aumenta sopravvivenza globale.

CLINICAL INVESTIGATION

Stomach

**INTRAOPERATIVE RADIOTHERAPY COMBINED WITH ADJUVANT
CHEMORADIOTHERAPY FOR LOCALLY ADVANCED GASTRIC ADENOCARCINOMA**

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LIHUA PENG, M.D.,* AND FEI XIONG, B.S.*

97 pz T3, T4, N+ sottoposti a gastrectomia totale o subtotale + LAD D2

51

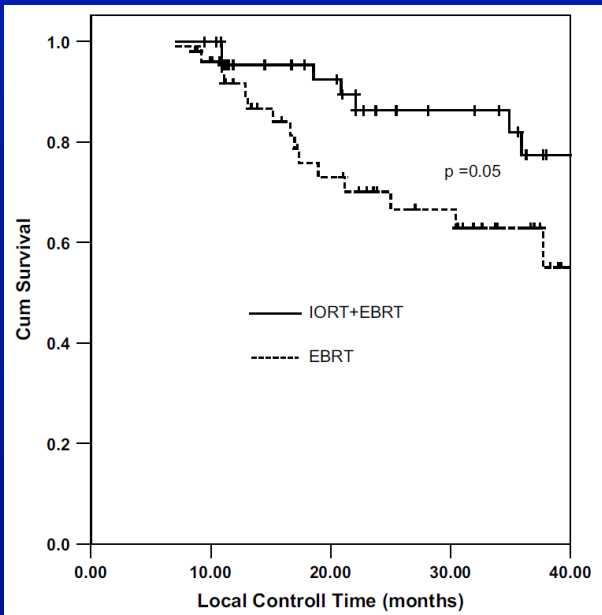
CHT + EBRT
1.8Gyx25 45Gy
(EBRT group)

46

IORT (range, 12–15 Gy) e
successivamente
CHT+ EBRT
1.8Gyx22 39.6Gy
(EBRT+IORT group)

Dimensioni campo IORT : 6x5-10x11cm

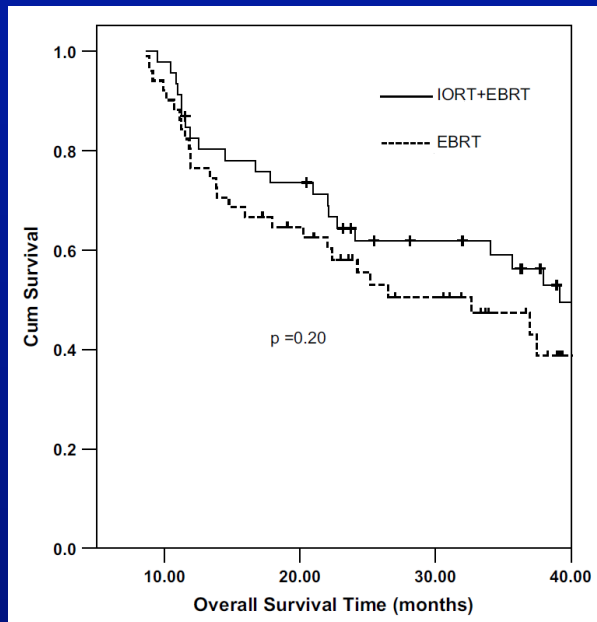
PTV IORT: LN tripode celiaco. Il letto tumorale non era incluso fatta eccezione per il sospetto da parte dei chirurghi di malattia residua.



LC

a 1, 2, e 3 anni era del 92%, 70%, e 63% nel gruppo EBRT e del 95%, 86%, e 77% nel gruppo IORT+EBRT

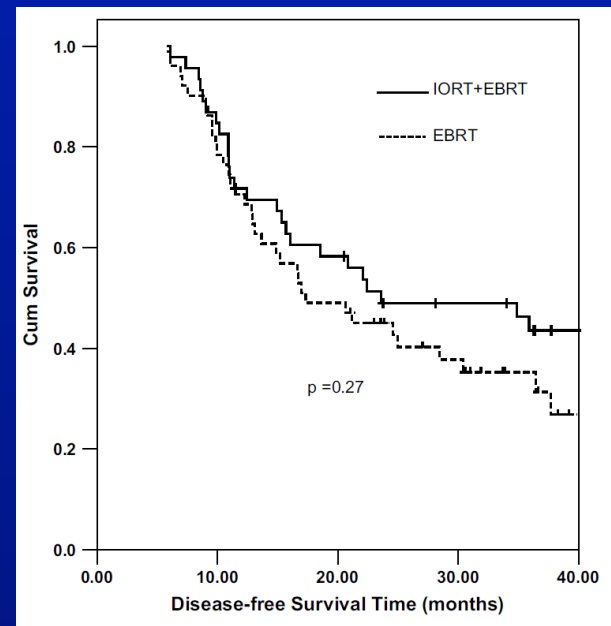
(p = 0.05)



OS

a 1, 2, e 3 anni era del 76%, 58% e 47% nel gruppo EBRT e del 83%, 64%, e 56% nel gruppo IORT+EBRT

(p = 0.20)



DFS

a 1, 2, e 3 anni era del 71%, 45%, e 36% nel gruppo EBRT e del 72%, 49%, and 44% nel gruppo IORT+EBRT

(p = 0.27)

| Adverse effects | EBRT | IORT+EBRT |
|----------------------------|-------------|------------------|
| Leukopenia G2 | 23 | 20 |
| Leukopenia G4 | 0 | 3 |
| Hematuria G4 | 1 | 0 |
| Digestive toxic effects G3 | 19 | 18 |
| Digestive toxic effects G4 | 0 | 4 |

L'uso della IORT seguita da chemioradioterapia adiuvante è efficace nel trattamento di adenocarcinoma localmente avanzato dello stomaco ed è ben tollerato

CONCLUSIONI (1)

(IMRT Limiti)

Distribuzione della dose

Basse dosi erogate ai reni: aumento di rischio di tossicità tardiva ? (>10-15 anni)

Tempo di trattamento

Tempi più lunghi: riduzione efficacia biologica della dose ? (riduzione dose rate)

Dose Integrale

Aumento di rischio di tumore secondario?

CONCLUSIONI (2)

I dati disponibili mostrano un miglioramento nella copertura del target senza riduzione della dose agli OAR

Nessuna riduzione della tossicità acuta

Nessun dato sulla tossicità tardiva

La RT 3D è associata ad una tossicità acuta e tardiva estremamente contenute

NESSUN BENEFICIO DALLE NUOVE TECNICHE !



GRAZIE PER L'ATTENZIONE