Community oncology working group: Optimal use of systemic therapy in the palliative setting

It’s time to stop: When to initiate palliative therapy

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ESMO 2014 Madrid

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I have no COI

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Agenda

- **Problem**
- Data
- Take home message

Cancer: the clinical problem

- Cancer incidence increases 2%/year Europe
  - 2006 - 3.2 million diagnosis
  - 2011 – 1.6 million deaths
- Half of cancer patients die of cancer
- Aging and comorbidities increase complexity
- End of Life (EoL) care is paramount
  - We make EoL decisions daily!

Cancer: the societal problem

- Patients and families when faced with cancer seek every possible chance
- There is emphasis on **cure** less on **chronicity**
- There is "space" and "market" for treatments/procedures that are not evidence based
- There are evidence based treatments/procedures whose evidence has been questioned
- Oncologists are making these decisions daily!

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Agenda

- Problem
- **Data**
- Take home message

I have been interested in this question:

WHY DO WE TREAT OUR PATIENTS WITH CHEMOTHERAPY UNTIL THE END OF LIFE?

Systemic therapy in the EoL

- Since the widespread use of systemic therapy at the end of life, we have reflected about it's utility or futility
- How much? With what consequences? Benefit? Why? Family, society, patient, physician?
- First, we characterized the problem in our Institution

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Systemic therapy in the EoL

Psycho-Oncology
Psycho-Oncology **16**: 863–868 (2007)
Published online 23 January 2007 in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/pon.1140

The aggressiveness of cancer care in the last three months of life: A retrospective single centre analysis

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Systemic therapy in the EoL

***Background*: There is concern that terminally ill cancer patients are over treated with chemotherapy, even when such treatment is unlikely to palliate symptoms. The study objective was to evaluate the use of chemotherapy in the last three months of life in a cohort of adult patients with advanced solid tumours.**

Prescription of palliative chemotherapy represents a very delicate equilibrium between toxicity and potential clinical benefit that is even more complex when treating patients with a short life expectancy, therefore there should be a clear definition of treatment goals. Simultaneously, the importance of high quality of end-of-life care, including symptom control, end-of-life decision making, choice of place of death, need for psychological and social support is increasingly valued by health care providers.

Braga, Psychooncology 2007

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Systemic therapy in the EoL

Table I. Cancer diagnoses of the overall population

Diagnosis	Number patients	%
Breast	101	31.7
Gynecological	47	14.7
Lung	38	11.9
Head and Neck (H & N)	31	9.7
Colorectal	27	8.5
Oesophagus and stomach	24	7.5
Melanoma	14	4.4
Urinary tract	13	4.1
Sarcoma	10	3.1
Pancreas	8	2.5
Other	6	1.9
Total	319	100

Cancer diagnoses of all 319 adult patients with solid tumours, other than primary CNS tumours, who died in 2003 and had received palliative chemotherapy.

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Systemic therapy in the EoL

- Any Chemotherapy?
  - 66% last 3 months - 211/319, 37% last month - 120/211, 21% last 2 weeks - 68/211
- How many CT regimens?
  - 75% one CT regimen - 159/211, 23% 2 regimens - 48/211, 2% 3 regimens - 2/211
- New Chemotherapy?
  - 50% last 3 months - 106/211, 14% last month - 30/211, palliative CT for 1st time - 28/30
- First Chemotherapy?

Braga, Psychooncology 2007

Systemic therapy in the EoL

- First ever palliative chemotherapy in the last three months of life?
  - 32% 1st ever palliative CT - 67/211
  - 2nd line - 10/67
  - 3rd line - 1

Table 3. Cancer diagnosis of patients that started palliative chemotherapy in the last three months of life

Primary tumour	Number of patients
Breast	19
Gynaecological	10
Lung	8
Head and Neck	6
Colorectal	4
Oesophagus and Stomach	3
Melanoma	3
Urinary tract	2
Sarcoma	2
Pâncreas	6
Other	4
Total	67

Braga, Psychooncology 2007

Systemic therapy in the EoL

- First ever palliative chemotherapy in the last month of life?
  - 13% - 28/211
    - 9 breast
    - 4 H&N
    - 4 lung
    - 3 cervical
    - 2 colon
    - 2 pancreas
    - 2 stomach
    - 1 ovary
    - 1 sarcoma

Braga, Psychooncology 2007

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Systemic therapy in the EoL

- In our center was there a correlation between disease and EoL CT ?

Table 2. Proportion of patients who received palliative chemotherapy

Diagnosis	Number of patients treated with chemo therapy	Total number of patients[a]	Proportion
Breast	101	118	0.86
Gynaecological	47	88	0.53
Lung	38	71	0.53
Head and Neck (H&N)	31	119	0.26
Colorectal	27	62	0.44
Oesophagus and Stomach	24	76	0.32
Melanoma	14	17	0.82
Urinary tract	13	33	0.39
Sarcoma	10	21	0.48
Pâncreas	8	16	0.5
Other	6	18	0.3
All	319	639	0.5

Number of patients who received palliative chemotherapy and overall number of patients who died in the same year with the same diagnosis in the cancer centre.[a] The determination of overall cancer centre death data were obtained from patient medical records only, without supplementation with death certificate data.

Braga, Psychooncology 2007

Systemic treatment in the EoL

- Emergency room visits? Hospital admissions? In the 211 pts
  - 80% had 1ER visit - 169/211
  - 37% last month - 120/211
  - 21% last 2 weeks - 68/211
- 15% of emergency visits were for treatment toxicity (67 visits: 32 hematological, 37 non hematological)
- 96% one hospital admission- 201/211
- 16% of admissions were due to toxicity (40 admissions: 29 hematological, 11 non hematological. 12 toxic deaths)

Braga, Psychooncology 2007

Systemic treatment in the EoL

- ICU admissions? In 5/211 pts (2%)
  - 2 surgical admissions
  - 3 medical admissions: pneumonia, hemorrhagic shock, septic shock (toxicity)
  - None were discharged alive
- Surgery? In 13/211 pts (6%)
  - 10 abdominal, 3 to CNS
  - None due to toxicity of treatment
- RT? In 50/211 pts (23%)
  - Mostly for symptom palliation
  - Median number of days until death 39 (range 0-90)

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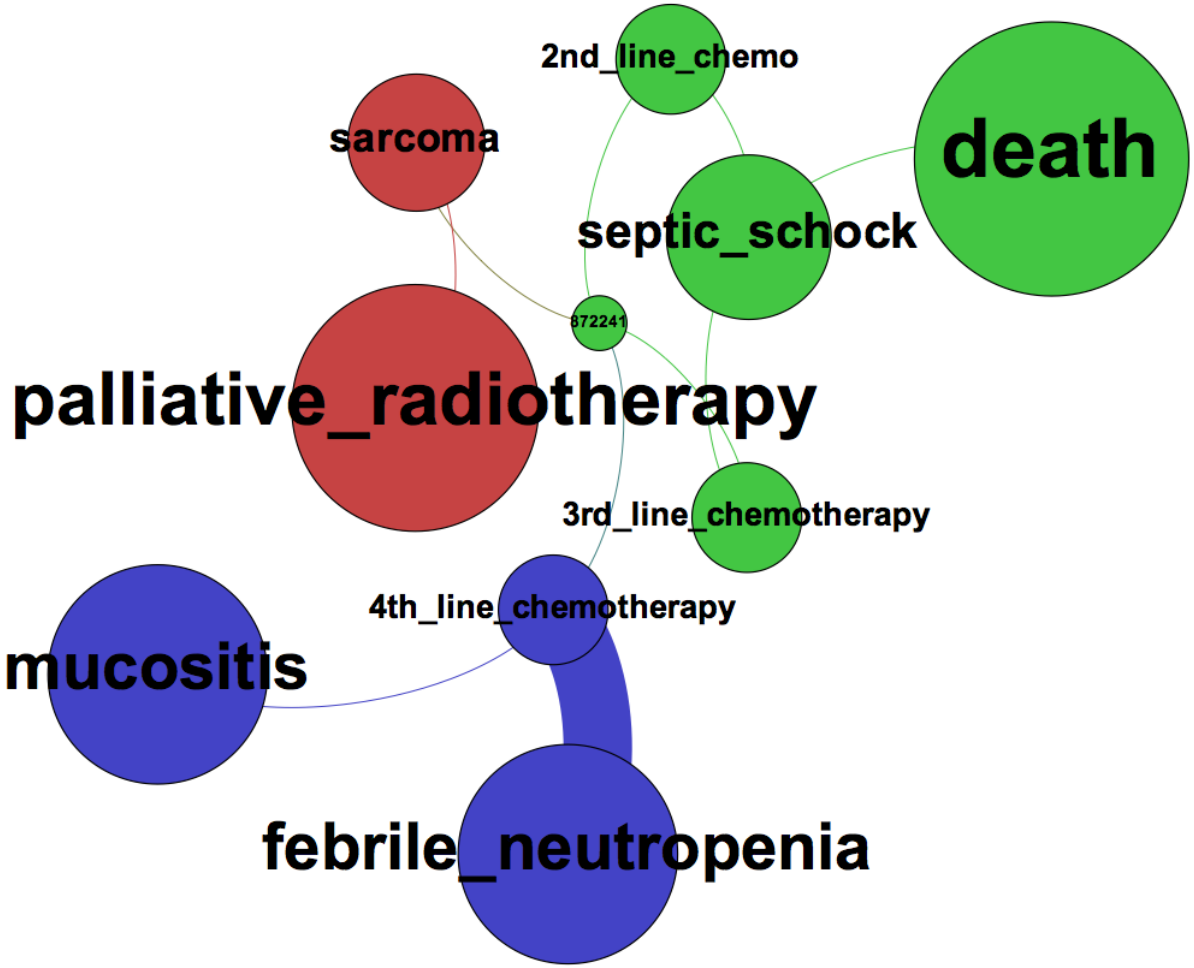
Unbiased view



Another reality: Same question

- We built two separate studies: Lung, breast. Why?
- We collected data on all chemotherapy, not just the last three months
- 200 patiens in each study
- The lung study would stand alone. Why?
- The breast group would be compared to the earlier study

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Population of lung cancer patients

Gender	n=223		%
Male	186		83.4
Female	37		16.6
Age at diagnosis (years)	n=223		
Mean		64.79	
Histology	n=223		%
Non Small cell	47		21.1
Adenocarcinoma	88		39.5
Squamous cell	56		25.1
Small cell	26		11.7
Large cell	3		1.3
Neuroendocrine	3		1.3
TNM Stage	n=221		%
I	3		1.3
IIA	4		1.8
IIB	7		3.1
IIIA	19		8.5
IIIB	50		22.4
IV	138		61.9
Number of CT lines	n=190		%
1	104		46.6
2	39		17.5
3	25		11.2
≥ 4	22		9.8
Performance Status 1st Line	n=190		%
0	18		8.1
1	83		37.2
2	60		26.9
3	28		12.6
Survival (months)			
Mean		11.79	
Median		8	
SD		12,9	

Lopes, Journal Thoracic Oncology (JTS) 2013

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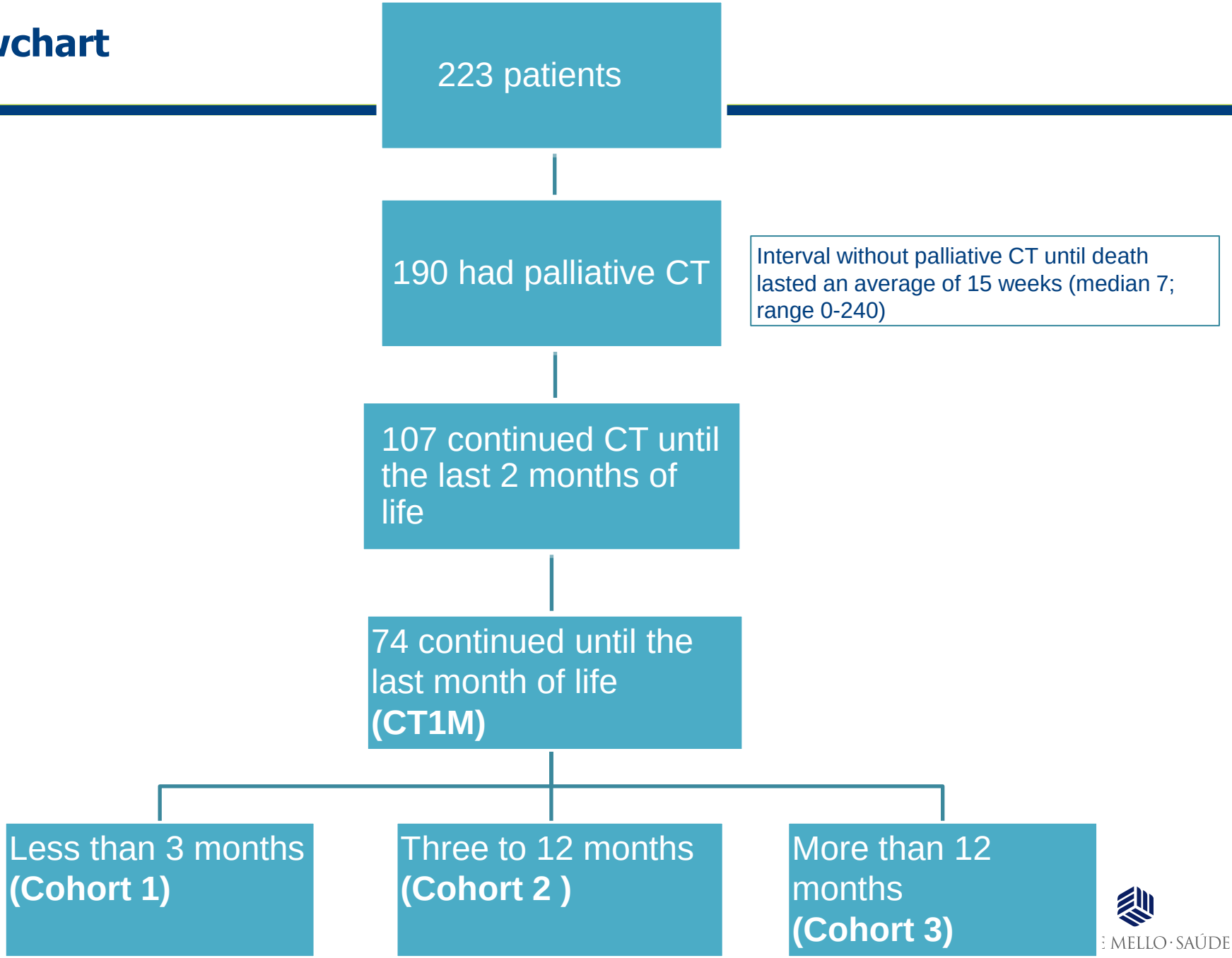
Flowchart



Lopes, JTS 2013

Population: last month

Gender	n=74		%
Male	60		81.0
Female	14		19.0
Age at diagnostic (years)	n=74		
Mean		63	
Histology	n=74		%
Non Small cell	63		85.1
Small cell	11		14.9
TNM Stage	n=74		%
IIA	1		1.4
IIB	1		1.4
IIIA	6		8.1
IIIB	14		18.9
IV	51		68.9
Overall Survival (months)			
Mean Median		7.58 4	
SD		9,9	

Lopes, JTS 2013

variables	Cohort 1 *(n=37)* n (%)	Cohort 2 *(n=23)* n (%)	Cohort 3 *(n=14)* n (%)
# regimens			
1	36 (97.3)	6 (26.1)	
2	1 (2.7)	10 (43.5)	3 (21.4)
3		6 (26.1)	7 (50.0)
4		1 (4.3)	3 (21.4)
5			1 (7.1)
PS 1st CT Line			
0	2 (5.4)	1 (4.3)	3 (21.4)
1	7 (18.9)	12 (52.2)	7 (50.0)
2	12 (32.4)	8 (34.8)	4 (28.6)
3	15 (40.5)	2 (8.7)	
4	1 (2.7)		
PS Last CT Line			
0	2 (5.4)		
1	6 (16.2)	6 (26.1)	5 (35.7)
2	13 (35.1)	7 (30.4)	6 (42.9)
3	15 (40.5)	10 (43.5)	3 (21.4)
4	1 (2.7)		
Toxicity on last treatment			
None or Mild	34 (91.9)	21 (91.3)	11 (78.6)
Important	3 (8.1)	2 (8.7)	3 (21.4)
Time response			
<3 Months	37 (100)	13 (56.5)	2 (14.3)
≥3 Months		10 (43.5)	12 (85.7)
Response on 1st CT regimen			
Some	3 (8.1)	10 (43.5)	10 (71.4)
None	33 (89.2)	12 (52.2)	4 (28.6)
N/A	1 (2.7)	1 (4.3)	
Response to any CT			
Some	3 (8.1)	10 (43.5)	13 (92.9)
None	33 (89.2)	13 (56.5)	1 (7.1)
N/A	1 (2.7)		
Patient/Family demands CT			
Yes	4 (10.8)	5 (21.7)	5 (35.7)
No	33 (89.2)	18 (78.3)	9 (64.3)

CT in the last month of life: Less than 3 month survival

- The pts that continued CT until the last month of life (CT1M) the median survival is half of the median survival of the whole sample;

- **The Patients that survived less than 3 months (Cohort 1)** 50% PS 3 or 4 and no CT responses;
- Only 8,1% had important toxicity in the last treatment with low contribution to PS deterioration;
- How are these patients?
  - CT naïve
  - advanced and symptomatic disease
  - low clinical improvement
  - absence of response to CT;

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Lopes, JTS 2013

CT in the last month of life: 3 to 12 month survival

- **Patients that survived between 3 and 12 months (Cohort 2)** showed an overall survival similar to the whole sample;
- How are these patients?
  - PS scores show deterioration through time
  - Patient's physical condition deteriorated
  - Low contribution from toxicity (important toxicity of 8,7%)
  - Patients with low disease burden
  - Patients with early disease course
  - Sensitive to CT
  - We found evidence of developing resistance (imaging)
- Why was CT was maintained?
  - Increased duration of response
  - Good PS scores

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Lopes, JTS 2013

CT in the last month of life: Over 12 months survival

- **The patients with more than 12 month survival (Cohort 3): Who are they?**
  - Overall survival superior to the whole sample
  - Had a better PS score at initiation and during CT
  - Important toxicity was higher and PS at last CT was worse than in the other groups
  - Patients responded to CT for more than 3 months but 70% was in first line of CT
- Why was CT was maintained?
  - Increased duration of response
  - Good PS scores
  - Increased survival

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Breast cancer

- Comparison of the two populations
- Total 232 patients

Comparative characteristics of BC		Initial cohort (n=118)	Recent cohort (n=114)
Age incidence	median (range)	60 (32-92)	60 (18-95)
Histology	Invasive carcinomas of no special type (NST)	110 (93%)	107 (94%)
	Lobular carcinoma	3 (2.5%)	3 (2.6%)
	Mucinous carcinoma	2 (1.7%)	2 (1.7%)
	Metaplastic carcinoma	2 (1.7%)	1 (0.9%)
	Medullary carcinoma	1 (0.9%)	1 (0.9%)
Disease stage at presentation	I (T1N0)	1 (0.9%)	2 (1.7%)
	II (T1-2 N1)	64 (54%)	68 (60%)
	III	22 (19%)	25 (22%)
	IV	31 (26%)	19 (17%)
ER status	positive	63 (53%)	56 (49%)
	negative	37 (47%)	44 (51%)
Treatment at presentation	Surgery	93 (79%)	83 (73%)
	Chemotherapy	94 (80%)	83 (73%)
	Radiotherapy	94 (80%)	90 (79%)
	Endocrine therapy	65 (55%)	56 (49%)
MBC	median survival (months)	24	20
Location of organ metastasis	Bone	36 (32%)	46 (40%)
	Locoregional	37 (30%)	35 (31%)
	Lung	24 (20%)	15 (13%)
	Liver	10 (9%)	11 (10%)
	Brain	4 (3.5%)	4 (4%)
	Ovaries & peritoneum	3 (1.7%)	3 (2.6%)

Palliation, location of death, systemic anti-cancer treatment and other aggressive care for MBC		Initial cohort (n=118)	Recent cohort (n=114)	p value of chi-square test for difference
Palliative interventions	Pain clinic	12 (10%)	58 (51%)	3.8×10^{-8}
	Palliative care consultation	5 (4.2%)	26 (23%)	1.6×10^{-4}
	Psychiatry	10 (8.4%)	18 (16%)	0.1
	Palliative radiotherapy	8 (6.8%)	63 (55%)	6.7×10^{-11}
Location of death	Hospital where was treated	108 (91.5%)	80 (70%)	0.04
	Another hospital	0 (0%)	5 (4.4%)	0.02
	Hospice	0 (0%)	16 (14%)	6.3×10^{-5}
	Home	2 (1.7%)	3 (2.6%)	0.6
	Unknown	8 (6.8%)	10 (8.8%)	0.6
Patients treated systemic anti-cancer therapy	15 days	32 (27%)	13 (11%)	0.004
	last month	45 (38%)	31 (27%)	0.1
	last 2 months	67 (57%)	49 (43%)	0.09
	last 3 months	80 (68%)	58 (51%)	0.06
Other indicators of aggressiveness in the patients treated in the last three months	Patients admitted	74/80 (93%)	53/58 (91%)	0.06
	Hospital admissions	284	174	2.7×10^{-7}
	Days in hospital	1725	1002	2.2×10^{-16}
	Patients ER visits	66/80 (83%)	51/58 (88%)	0.16
	Emergency room admissions	166	201	0.06
	Intensive care unit admissions	2 (2.5%)	0	0.15
Patients starting treatments in the last three months	A new regimen	38 (32%)	28 (24%)	0.2
	A 2nd regimen	6 (5%)	2 (1.7%)	0.1
	First ever regimen for MBC	19 (16%)	5 (4.4%)	0.004

Guerra, under revision

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How long do we treat these patients?

Recent cohort (n=114)	Systemic therapy data
No systemic therapy	28 (25%)
1 regimen	18 (16%)
2 regimens	16 (14%)
3 regimens	14 (12%)
4 regimens	10 (8.8%)
5 regimens	5 (4.4%)
6 regimens	23 (20%)
Median regimens	2

Guerra, under revision

What happens with each subsequent CT regimen?

Systemic therapy regimens, recent cohort (n=114)	Median duration of regimens & range (days)	Number treated patients (% of population)	Number of patients w/response or stable disease (%)	Number of patients w/ progression (%)
1st	87 (1-736)	86 (75%)	22 (26%)	64 (74%)
2nd	92 (1-562)	68 (60%)	20 (29%)	48 (70%)
3rd	96 (7-1360)	52 (46%)	13 (25%)	39 (75%)
4th	54 (1-511)	38 (33%)	10 (26%)	28 (74%)
5th	67 (1-790)	27 (24%)	4 (15%)	23 (85%)
6th	59 (1-331)	23 (20%)	3 (13%)	20 (87%)
p-value chi square test	0.001	$5.5x10^{-12}$	0.08	0.7

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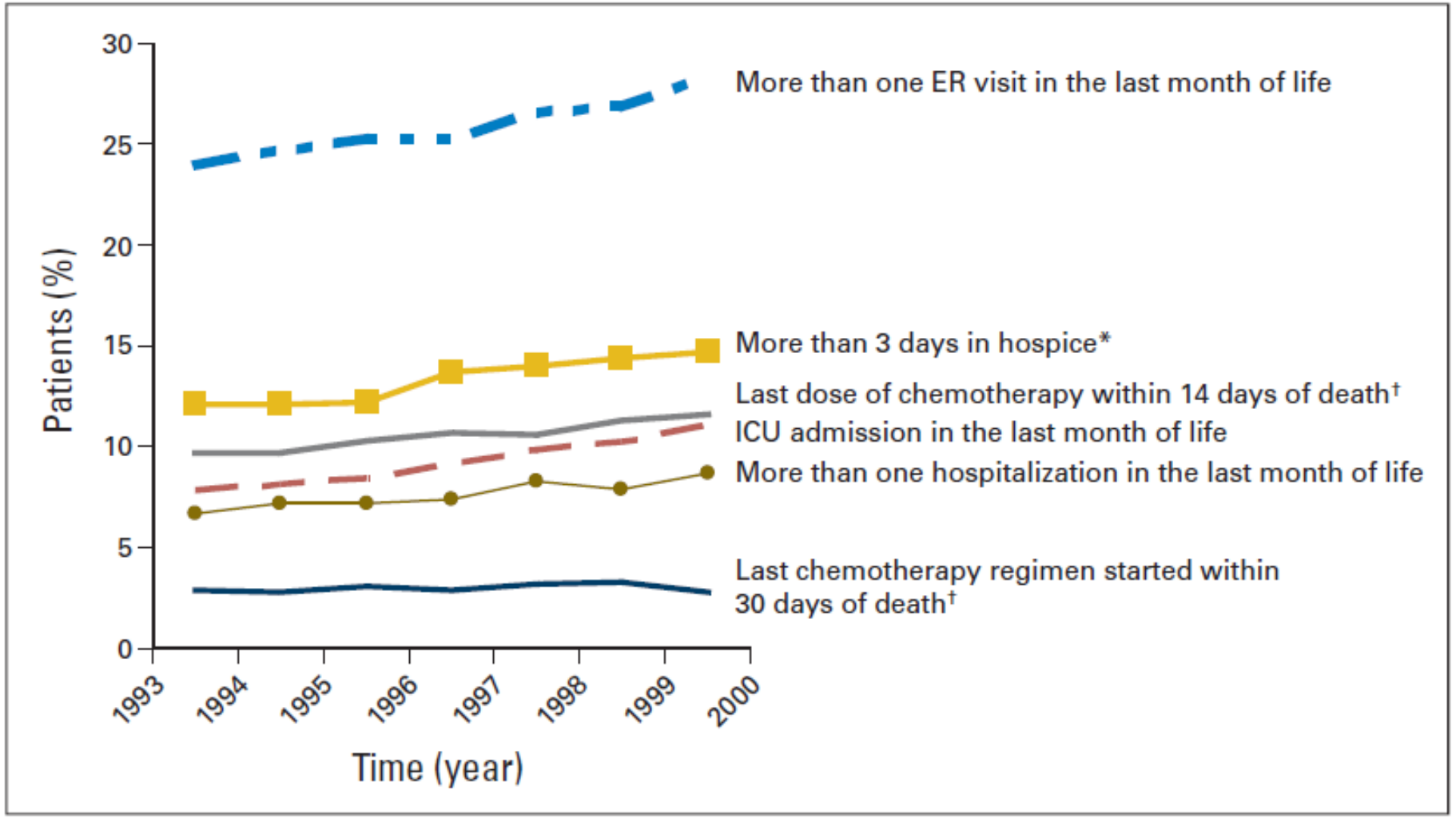
Guerra, under revision

The bigger picture



Earle, JCO 2008

Agenda

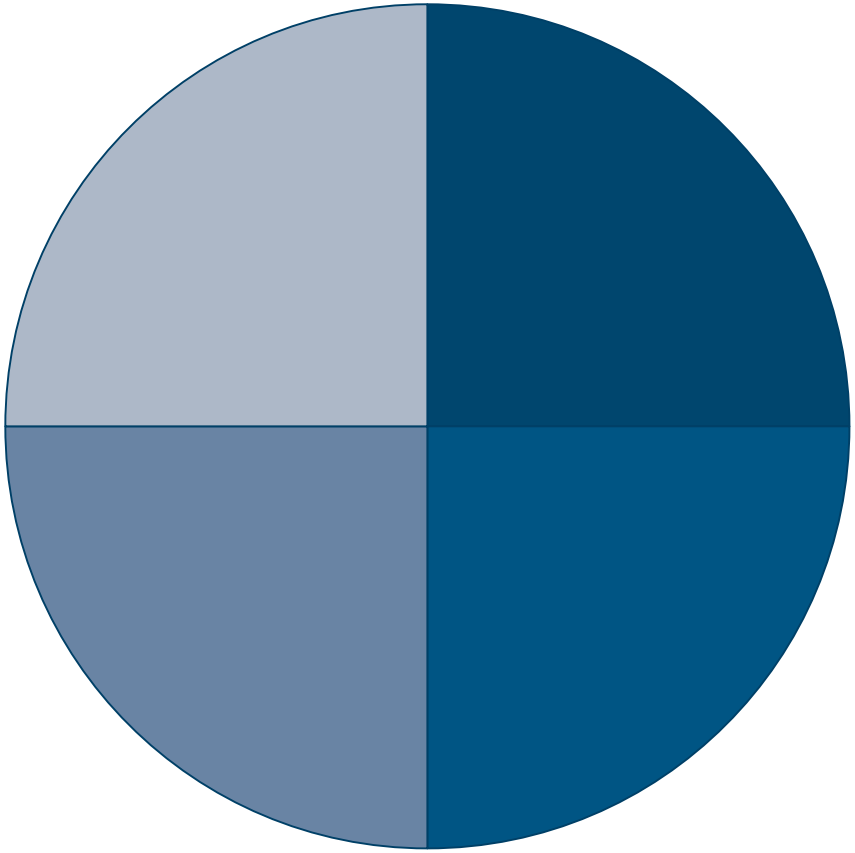
- Problem
- Data
- **Take home message**

To conclude: My opinion

- We need **research: prospective studies** in the EoL of patients STILL on CT
  - We need to understand why and to question our actions
- We must **listen** more: There is evidence (Berry JCO 2011) that presenting symptoms and quality of life evaluations to oncologists before consultation increased discussion about these issues (p=0.032)
- We must **teach** our patients more: There is evidence that our incurable patients think they are curable (Weeks NEJM 2011)
  - But how can we listen/teach if we have 15 minute consultations? Timed by hospital administrations
- We must **discuss** more among ourselves in teams: There is evidence that patients cared for in University hospitals have less CT in the last two weeks of life that those cared for by oncologists (Earle JCO 2008)
- We should we have more **integration** with palliativists: The integration of palliative care increases QoL and survival (Zimmermann Lancet 2014, Temel NEJM 2012)

Take 4 ideas home

Should I STOP palliative CT?



- Listen to your patients
- Teach your patients
- Discuss among colleagues
- Integrate care with palliativists

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THANKS!

- To the presenters before me
- To my students: Nuno Guerra Pereira
- To my residents: Fábio Lopes
- To my mentors
- To my colleagues: H2020 project
- To patients

- For your attention
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