Disparities between survival data derived from clinical trials and epidemiological studies

Pr Jean FAIVRE
(Dijon)

Conflict of interest: none

Clinical studies (randomised studies)

- allow to define the optimal therapeutic strategy
- are needed to authorise the use of new treatments
- usefull to compare treatment and to define gold standard

Clinical studies (limits)

Recruitment biased by the selection of patient:

- **Frequent exclusion of elderly patients**
- **Absence of comorbidity**
- **High socioeconomic status**
- **Selected expert centers**
- **…**

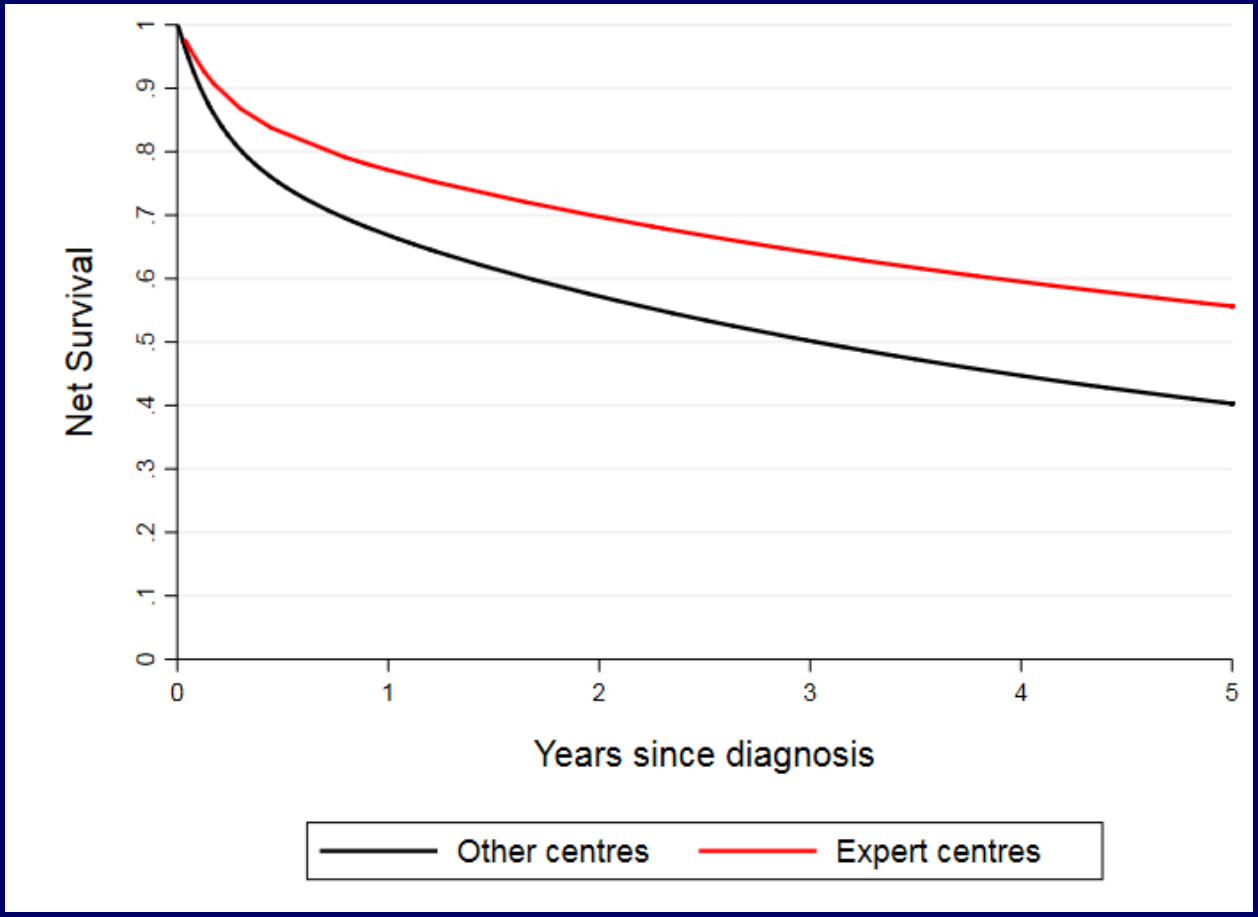
Epidemiological studies

- include all cases diagnosed in a well defined population
- allow to know how patients are treated in everyday life
- represent the only way to assess real management and outcomes
- allow to compare survival over time with other registries using the same methodology
- allow to study how recommandations have spread

Burgundy Cancer Registry (population: 1 million)

- 2000-2011: 288 cases
- Using 2000 WHO classification
- 31% treated in referent centres
- Five-year net survival: 51%

Survival of NETs according to the sector of care



62%

42%

Characteristics of patients according to sector of care

	Expert centres	Other centres	
Ages			
<75	82%	65%	
≥75	18%	35%	*p* <0.003
Site			
Gastrointestinal	53%	65%	
Pancreatic	39%	22%	
Other	8%	14%	*p* <0.007
Stage at diagnosis			
M0	44%	39%	
M1	56%	61%	*p*=0.314
Charlson			
0	61%	59%	
≥1	39%	41%	

Factors influencing survival: 2000-2011 period (multivariate analysis)

		Hazard ratio	IC 95%	*p*
Sector of care				
	Expert centres	1		
	Other centres	1.61	(1.04-2.5)	0.040
Sex				
	Males	1		
	Females	0.67	(0.47-0.96)	0.030
Age				
	<75	1		
	≥75	1.66	(1.12-2.45)	0.011
Site				
	Gastroenterointestinal	1		
	Pancreatic	1.41	(0.94-2.12)	0.096
	Other	1.61	(0.99-2.61)	0.005
Stage at diagnosis				
	M0	1		
	M1	6.60	(3.59-12.14)	<0.001

Epidemiological studies allow to compare survival of NETs according to country

Northern Europe	60%
Western Continental Europe	54%
UK	43%
Eastern Europe	38%
All	48%

Lepage C et al Gut 2014

Epidemiological study allow to evaluate how recommendations have spread

	< 70	≥70
Local Excision	17%*	10%*
Chemoradiation	65%*	30%*
Radiotherapy	17%	60%

* Treated following recommendations

Epidemiological studies (limits)

- do not allow to interpret differences in survival according to treatment modalities because the selection of patients is not related to hasard

- difficulty to collect complete data

- changes in classification difficult to implement

Survival for anal canal cancer among patient treated for cure

	5-year net survival
Chemoradiotherapy alone	79%
Chemoradiotherapy before abdominoperineal resection	63%
Radiotherapy	44%
Local excision	98%

Disponibility of data to define grade in Burgundy

	2009-2013	2014-2015
Ki 67	69%	85%
Differentiation	not available	51%

Problem of the quality of data available to cancer registries

- **RARECARE: 2115 gastrointestinal NETs, 353 had adequate information on behaviour**

- **PRONET study: 59 laboratories**

19: 1 to 10 cases; 31: 31 to 50 and 9 over 50

Trama et al Tamori 2017
Scoazec et al Neuroendocrinology

Neuroendocrine tumours classifications

- Up to 2000 registration based on morphology codes (IDC-03) with a malignant behaviour
  Stage at diagnosis defined according to the classic TNM
- 2000: classification pools digestive carcinoids and pancreatic endocrine tumours, include NEC , well differenciated Net & WD carcinomas
- 2004: New classification of lung NET
- 2007: Introduction of grading system in 3 categories by ENETS
- 2009: TNM classification defining T by size and site
- 2010: new WHO classification with slight difference between ENETS and WHO classification
- 2017: New WHO classification defining grade G1 by a Ki 67 under 3% and grade G3 by a well differentiation and Ki 67>20% for pancreatic tumours

NETs and cancer registries

- The aim of Cancer registries is to collect cancer cases with a malignant behaviour (/3).
- Some NETs with benign behaviour could have recurrence up to 10 years after diagnosis
- Cancer registries could be used to define the pathological risk factors in order to identify discriminant outcome factors.

Social consequences of classifying all NETs among cancer

- Insurance and credit surtax are applied, in France, to cancer patients

- Patients treated for cure for a well differentiated NET, recurrence-free 3 years after diagnosis can be considered statisticaly cured

Conclusion

- There are no disparities between survival data derived from clinical and epidemiological studies
- Differences are only related to selection bias
- They provide complementary data for the management of NETs which must be interpreted with caution