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French Multicentric Prospective Evaluation of Dynamic Contrast-enhanced Ultrasound for the Evaluation of Antiangiogenic Treatments

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Aims

Early functional evaluation of new treatments in oncology is of major importance as the treatments' efficacy must be ascertained as soon as possible. Since new therapies often induce lesion necrosis without reducing tumor volume international oncology and radiology experts have pointed out that the morphological criteria currently used for solid tumors are no longer pertinent. As there is currently no consensus regarding the parameters or the timing for early evaluation of anti-angiogenic drugs, this project aims to suggest new criteria for functional ultrasound imaging for early evaluation of new targeted therapies.

Methods

A new methodology to quantify tumor perfusion with DCE-US

At Gustave-Roussy Institute functional imaging Dynamic Contrast-enhanced Ultrasound (DCE-US) is used to quantify tumor perfusion. This technique allows evaluation of:

- blood flow: BF
- blood volume: BV
- mean transit time: MTT = BV/BF

In several published studies we were able to confirm the efficacy of DCE-US as early predictor of tumor treatment response.

We developed a new methodology to calculate perfusion: After bolus injection of Sonovue (Bracco), we automatically acquire 3 minutes of raw data with an ultrasound system (Toshiba Aplio and I-Assist). These data are analyzed on an UltraExtend workstation to assess the time intensity curve on the 3 minutes of raw data using a mathematical model (patent PCT/IB2006/003742) to automatically obtain 7 perfusion parameters (Fig 1).

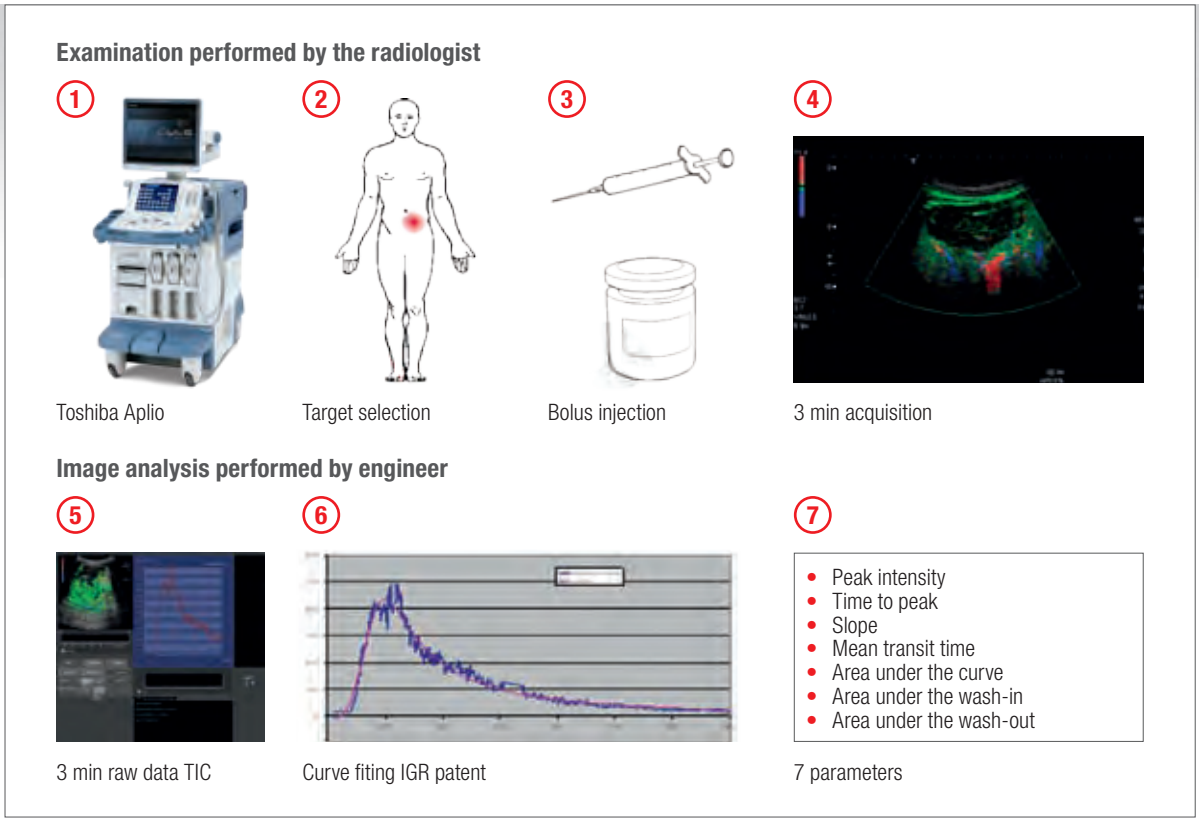

Fig. 1: DCE-US methodology to quantify tumor perfusion.

French national DCE-US programme

In October 2007, a large French national DCE-US study was launched, sponsored by the Ministry of Health (INCA) and partly by Toshiba and Bracco.
The objectives of this study are:

- to extend and validate our methodology using raw linear data,
- to determine the best parameter and the decisive timing for anti-angiogenic therapies response evaluation, N. Lassau [1]
- to demonstrate the feasibility of DCE-US in 20 hospitals in France, J. Pellier [2]
- to assess the economic impact of DCE-US with a prospective cost study, J. Bonastre [3]

20 centers joined this project (Fig 2) Gustave-Roussy Institute, with Dr Lassau as principal investigator 11 comprehensive cancer centers and 9 teaching hospitals.
65 radiologists participate and use the methodology developed by IGR (Fig1).
650 patients treated with anti-angiogenic therapies (Fig 3) will be included in the study, with different types of lesions (Fig 4, metastasis of RCC, colon cancer, melanoma, GIST, breast cancer and primary tumors HCC).
All patients will be evaluated with DCE-US at baseline, D7, D15, 1 month, 2 months, and a CT-scan will be performed at baseline and every 2 months (Fig 5) to correlate our results to RECIST criteria.

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Clichy – Hôpital Beaujon: Valérie VILGRAIN
Boulogne Billancourt-Ambroise Paré: Sophie CHAGNON
Paris – CHU de la Pitié-Salpetrière: Olivier LUCIDARME
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Marseille . Paoli Calmettes: Antony SARRAN
Clermont-Ferrand – Centre Jean Perrin: Yvette PTAK
Lyon – Hôtel Dieu: Denis MARION

Fig. 2: Participating centers

Histological type	Nb of patients	%
Metastatic renal cell carcinoma	143	30
Hepatocellular carcinoma	96	21
Metastatic colorectal cancer	57	12
Metastatic melanoma	50	11
Metastatic GIST	48	10
Metastatic breast cancer	40	9
Other site	33	7
Total number of patients	467	100

Fig. 4: Current distribution of lesions in the multicentric study.

Main treatments	
Sorafenib	126
Bevacizumab	95
Sunitinib	88
Imatinib	37
Other / combinations	55

Fig 3: Distribution of anti-angiogenic therapies in the multicentric study.

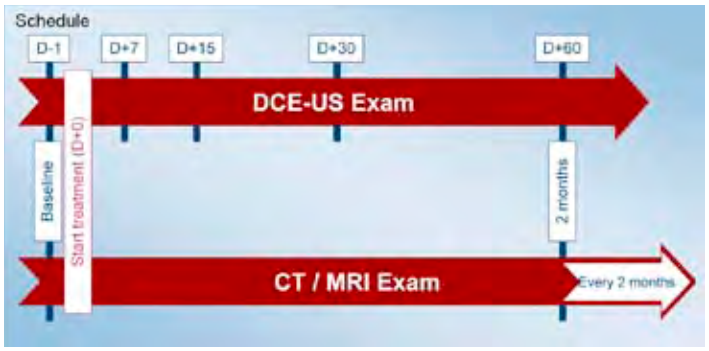


Fig 5: Examinations schedule.

Results

Perfusion parameters – Nathalie Lassau

Based on this new methodology, in 2009 we presented at ASCO [4] the results of a population of 117 patients, with 801 DCE-US examinations. Each of the 7 parameters was evaluated with RECIST criteria (Fig 6). The results show that for different types of tumor undergoing targeted therapy AUC and AUC wash-out are reliable means of analyzing tumor perfusion and predicting treatment response.

Clinical results of the French multicentric study - Nathalie Lassau

For this analysis, 401 patients were included with 1097 DCE-US performed (current number of patients: 480 and 1600 DCE-US).

3 parameters significantly correlated with relapse at 2 months: AUC, AUC wash-in, AUC wash-out (Fig 7). Comparison of parameters in responders and non-responders with Kruskall-Wallis tests shows a good prediction of response at 6 months with the AUC parameter.

This study confirms the importance of the variation in the AUC and AUWO after 1 month.

The final study including 650 patients with a longer follow-up, will determine a cut-off to discriminate responders and non- responders

Parameters	HCC Avastin	RCC Sutent	GIST Masatinib	Phase I: Nexavar DTIC
Patients = 117	42	38	20	17
DCE-US = 801	263	168	263	117
AUC	**0.03**	**0.008**	**0.004**	**0.04**
AUC Wash-in	0.03	NS	0.002	0.01
AUC Wash-out	**0.02**	**0.01**	**0.002**	**0.04**
Slope	NS	0.0005	0.003	NS
Peak intensity	NS	0.0005	0.003	0.02
TTP	NS	0.002	0.005	NS
MTT	NS	0.007	NS	NS

Fig. 6: Reliability of perfusion parameters.

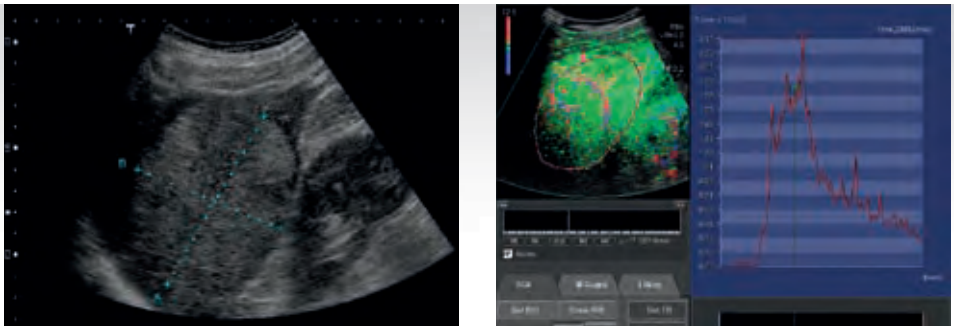
Parameters	D -1	D +7	D +15
AUC	p= 0.04	p=0.0006	p=0.02
AUWI	p=0.03	p=0.003	p=0.04
AUWO	p=0.04	p=0.0004	p=0.03

Fig 7. Prediction of relapse at 2 months.

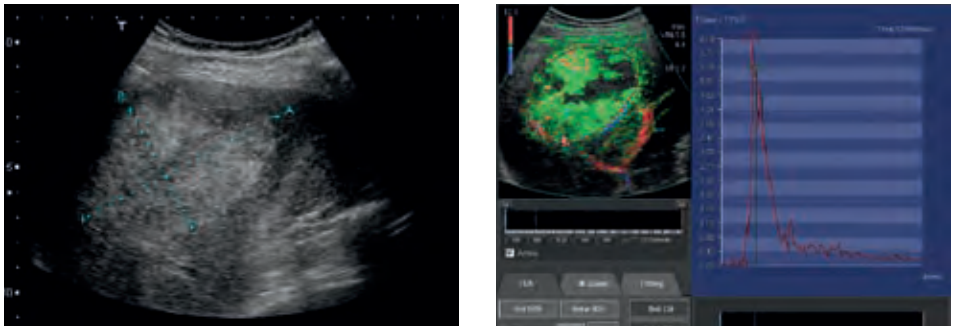
DCE-US at D30 Variation: D-1/D30	P value	Variation in responders	Variation in non-responders
AUC	0.003	**–80%**	**–40%**
AUWI	0.009	–70%	–50%
AUWO	0.003	–81%	–41%
PI	0.002	–74%	–45%
Slope	0.001	–81%	–49%

Fig. 8: Comparison of parameters in responders and non-responders.

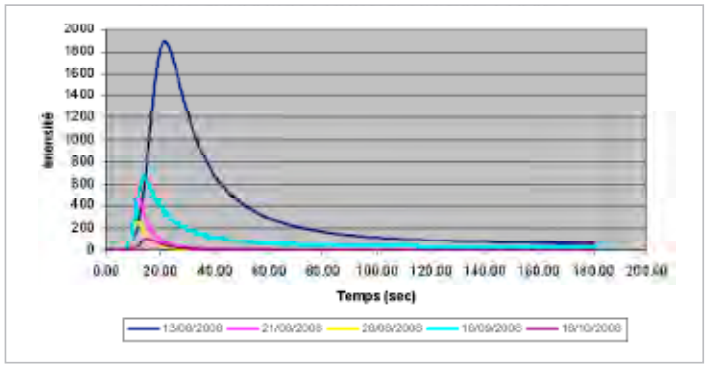
Clinical case 1:
Patient with hepatic metastasis from renal cell carcinoma: m-Tor inhibitor + Avastin.



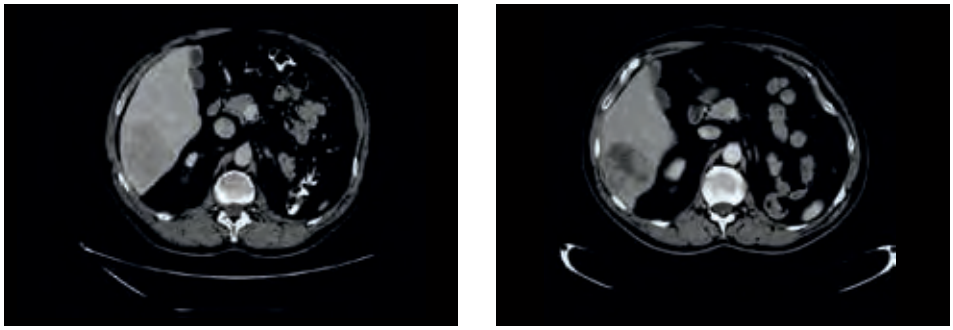
DCE-US at baseline.



DCE-US at D7.

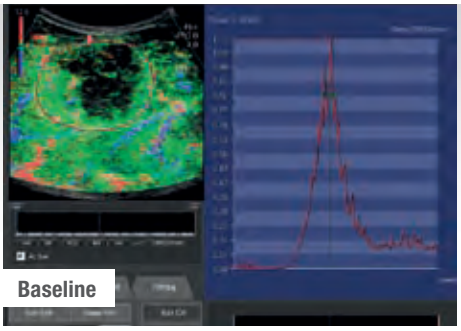


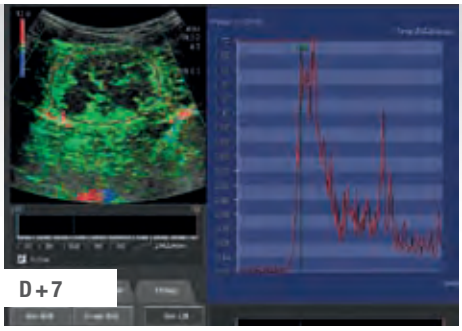
Evolution of contrast uptake curves: baseline, D7, D15, 1 month, 2 months.

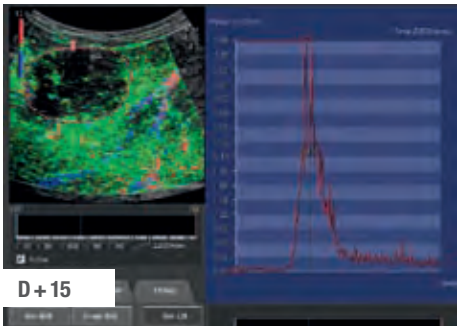


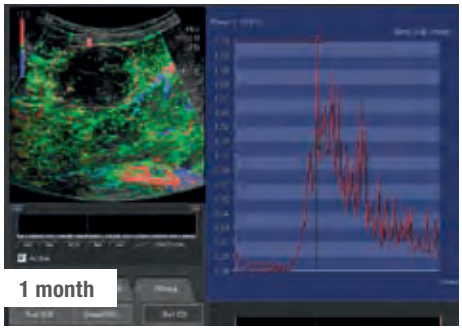
CT-scan at baseline and after 2 months.

Clinical case 2:
Patient with hepatic metastasis colon cancer treated with a combination of chemotherapy + Avastin.

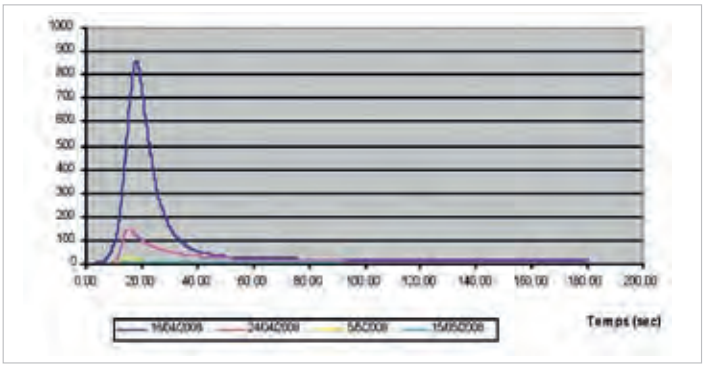




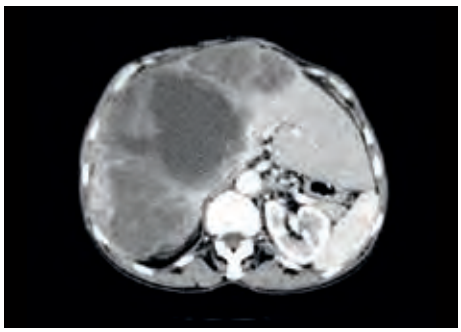


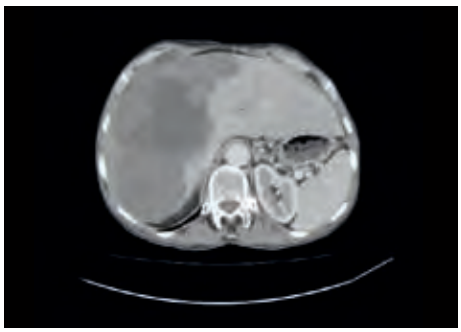


DCE-US at baseline, D7, D15, 1 month.



Evolution of contrast uptake curve.





CT-scan at baseline and after 2 months.

Evolution of DCE-US examination quality – Julien Pellier [2]

The objective was to assess the evolution of the DCE-US examination quality in a large multi-centric study and to analyze the radiologists' experiences.

The first point was to define a quality score for each DCE-US exam.

We used the following criteria: size of lesion, definition of the borders and motion of the lesion during the 3 minute acquisition (Fig 9).

A total of 1600 exams (470 patients) was analyzed with these criteria.

For 1459 examinations a quantification was performed. For the 141 remaining exams the quantification was not possible due to technical reasons (reference images not available, less than 1 minute of recording, target almost never in acoustical window, etc.)

The distribution of quality scores demonstrates that 85% of examinations have a quality score ≥2 (Fig 10). This score will be considered as the threshold for good quality.

The analysis of mean time needed to quantify an exam shows that increased quality leads to faster image analysis (Fig 11).

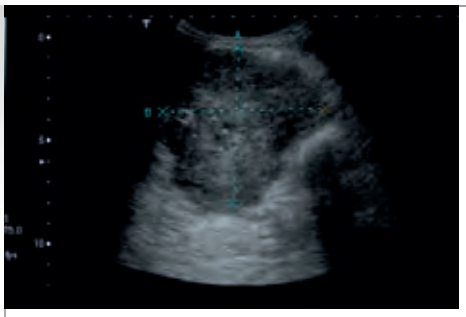
The second aspect was to evaluate the quality score according to the radiologist's experience (Fig 12). We demonstrated that the quality score increases with number of exams performed by a radiologist.

Then, we analyzed 2 independent parameters (number of exams and lesion's site) which have an impact on exam quality. We used a logical regression applied to the variable of interest: quality score ≥2, and the 2 parameters:

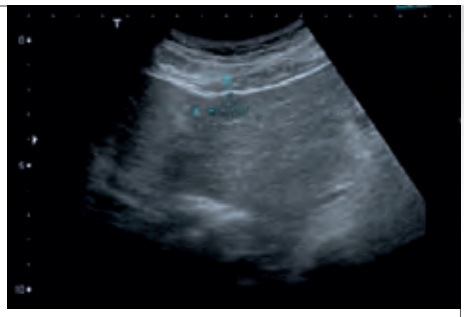
- Number of exams: experienced radiologist >10 exams
- Site of the lesion: other versus liver

The results show that the quality score increases by 1.58 when the radiologist has performed more than 10 exams, and it is almost double if the selected site is not in the liver. Site selection is very important, as other sites (mostly superficial lesions) have very low motion compared to liver (breathing motion).

In 50% the target lesion was in the liver, in the other 50% the lesions were located in the lymph node, peritoneal, pelvis, etc.



Big target. Well define borders. No motion.



Small target. Blurry borders. Motion.

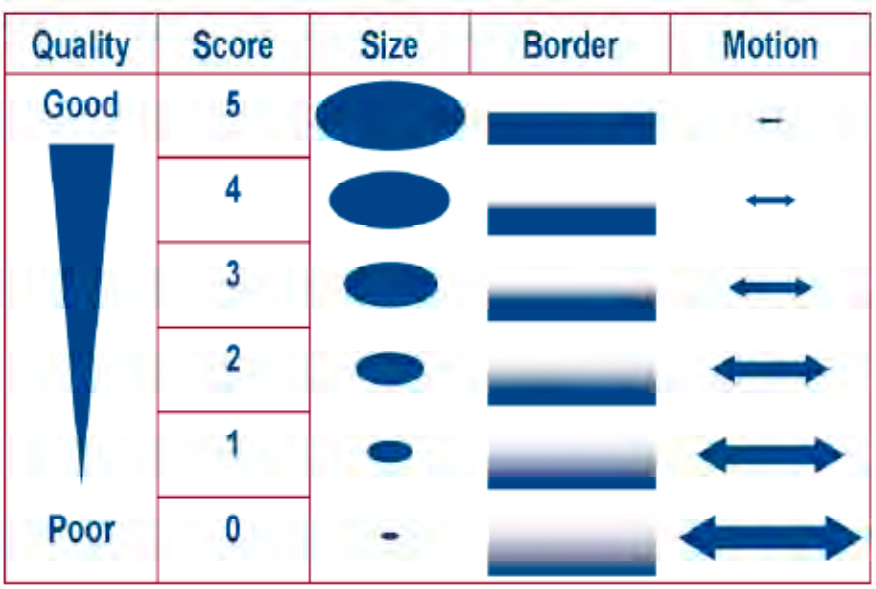


Fig. 9: Quality score definition.

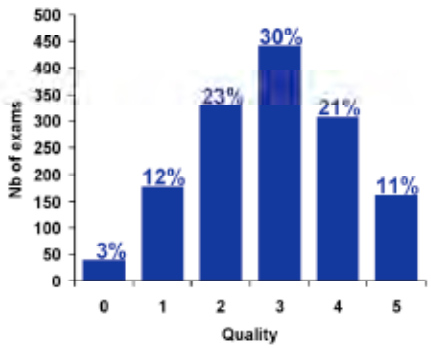


Fig. 10: Quality score distribution.

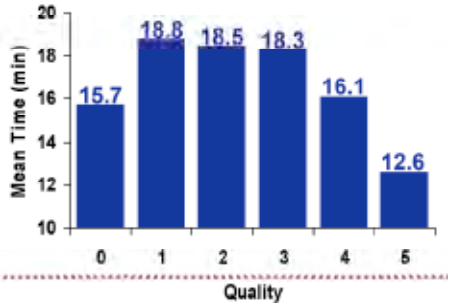


Fig. 11: Mean time analysis.

Results of cost analysis in the multicentric study – Julia Bonastre

Another goal of this multi-centric study was to assess the cost of DCE-US in a large population of patients and centers, to analyze cost variability and to compare cost and reimbursement in a French setting.

Methods

Total cost (TC) was assessed from the hospitals' point of view, and all data were collected prospectively for each exam. Total Cost included the following components:

TC = staff + contrast agent + equipment + logistics + overheads

- The resource data collected prospectively for each exam include procedure duration and staff inputs: radiologist, assistant (radiation technologist or nurse), biomedical engineer and medical secretary.
- The contrast agent (Sonovue®, Bracco) encompassed the number of injections in case of several injections for one examination
- The equipment cost include acquisition and maintenance of Toshiba Aplio
- Valuation of the use of resources: unit costs data from Gustave-Roussy Institute

Results

The total cost of a DCE-US examination including quantification was €182 (US$ 273), with half of the cost attributed to the contrast agent (Fig 16). Low cost variability (Fig 17) on such a large multi-centric study was interesting as was the fact that with 23 minutes the radiologist's intervention per exam is close to a conventional US examination (Fig 14).

Currently there is no specific reimbursement code for DCE-US in France. In practice, the conventional US code corresponding to € 76 is used. The extra cost of € 106 per exam is borne by the hospital. This study provides information to serve as a basis for reimbursement by the national health insurance funds.

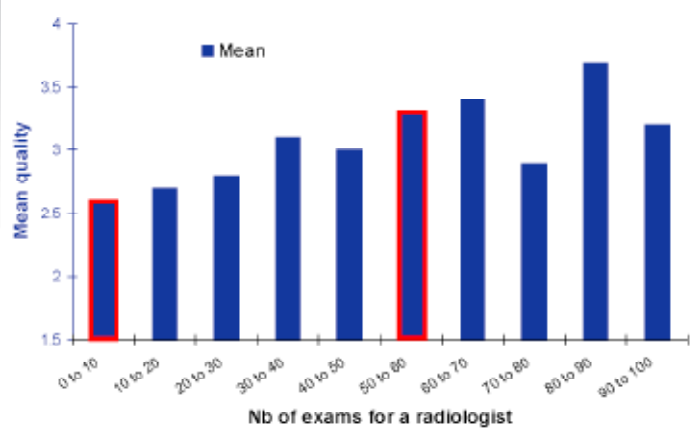


Fig. 12: Quality evolution with number of examination.

Odds ratio estimation			
Parameter	**Estimate point**	**95% Wald confidence interval**	
> 10 exams	**1.58**	1.26	2.15
Other sites	**1.93**	1.42	2.61

Fig. 13

Resource use per DCE-US procedure	
Procedure duration	28 min
Radiologist's intervention	23 min
Quantification of perfusion parameters	17 min

Fig. 14: Resource per DCE-US procedure.

Contrast agent bolus injections	
Average number per exam	1.1 (min = 1, max = 3)
2nd bolus injection	In 10 % of exams (18% of baseline and 7% of subsequent)

Fig. 15: Mean contrast injections.

Cost components	€	%
Staff	54	30
Contrast agent	88	48
Equipment	10	6
Logistics & overheads	30	16
Total cost	**182**	**100**

Fig. 16: Cost distribution.

Cost variability analysis		
Coefficient of variation	23%	Small
Extra cost	in 10% of exams	due to reinjection
Sensitivity to main costs drivers	contrast agent price	and reinjection rate
Mean DCE-US cost range	**€ 169 to € 210**	

Fig. 17: Cost variability.

References

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