Cancéropôle Grand Sud-Ouest

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DETERMINATION OF OXALIPLATIN DOSE IN ADJUVANT CHEMOTHERAPY : VALIDATION OF A DEDICATED SOFTWARE BASED ON INITIAL CT SCAN

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UNICANCER

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BACKGROUND 1

- Current worldwide standard of care for patients with stage III CRC is 6 months of adjuvant chemotherapy with fluoropyrimidines and oxaliplatin. [1-3]
- Oxaliplatin causes chronic neurotoxicities that can severely affect quality of life and reduce activities of daily living. [1, 2]

[1] André T et al. Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004 Jun 3;350(23):2343-51

[2] Kuebler JP et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol. 2007 Jun 1;25(16):2198-204

[3] Haller DG et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol. 2011 Apr 10;29(11):1465-71

BACKGROUND 2

Evidence suggests that body composition, such as sarcopenic obesity, might be predictive of chemotherapy toxicity.

- ✓Lean body mass (LBM) may be useful to normalize chemotherapy doses. [4]
- ✓A recent cohort of CRC patients treated with FOLFOX regimens using conventional BSA-based showed low LBM was a significant predictor of neurotoxicity. A cut point of 3.09 mg/kg for developing toxiciy was determined by ratio (oxaliplatin dose according to BSA) / LBM. [5]

[4] Prado CM et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008 Jul;9(7):629-35

[5] Ali R et al. Lean body mass as an independent determinant of dose-limiting toxicity and neuropathy in patients with colon cancer treated with FOLFOX regimens. Cancer Med. 2016 Jan 27

BACKGROUND 3

CT is a reliable imaging method for body composition analysis :

- ✓once L3 region is identified, analysis software is used to identify specific tissue demarcation using Houndsfield unit thresholds established for bone, skeletal muscle, visceral and adipose tissues.
- ✓LBM is then calculated according to skeletal muscle surface. [6]

>> SliceOmatic, TomoVision, Montreal, Quebec, Canada

[6] Mourtzakis M et al. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008 Oct;33(5):997-1006

BACKGROUND 4

According to french recommandations, TAP CT-scan is warranted for initial imaging evaluation in patient diagnosed with colorectal cancer (CRC).

> « Le bilan d'imagerie repose sur la tomodensitométrie thoraco-abdominopelvienne, avec injection de produit de contraste.»

GUIDE ALD - Colorectal cancer, February 2008

PURPOSE

Validation of a software dedicated to determination of lean body mass and calculation of oxaliplatin dose, based on initial CT scan

>> Myrian, Intrasense, Montpellier, France

MATERIALS AND METHODS

Study population and design

- 101 patients from a nutrition and oncologic database
- Baseline body composition was defined at initial stage disease :
  - - Weight
  - - Height
    - ✓→body surface area (BSA) (DuBois & DuBois formula)
    - ✓→body mass index BMI
- « daily practice »oxaliplatin dose according to BSA was calculated

  $Doxa^{BSA} = (85mg/m^2 \times BSA)$

MATERIALS AND METHODS

Body composition measurements

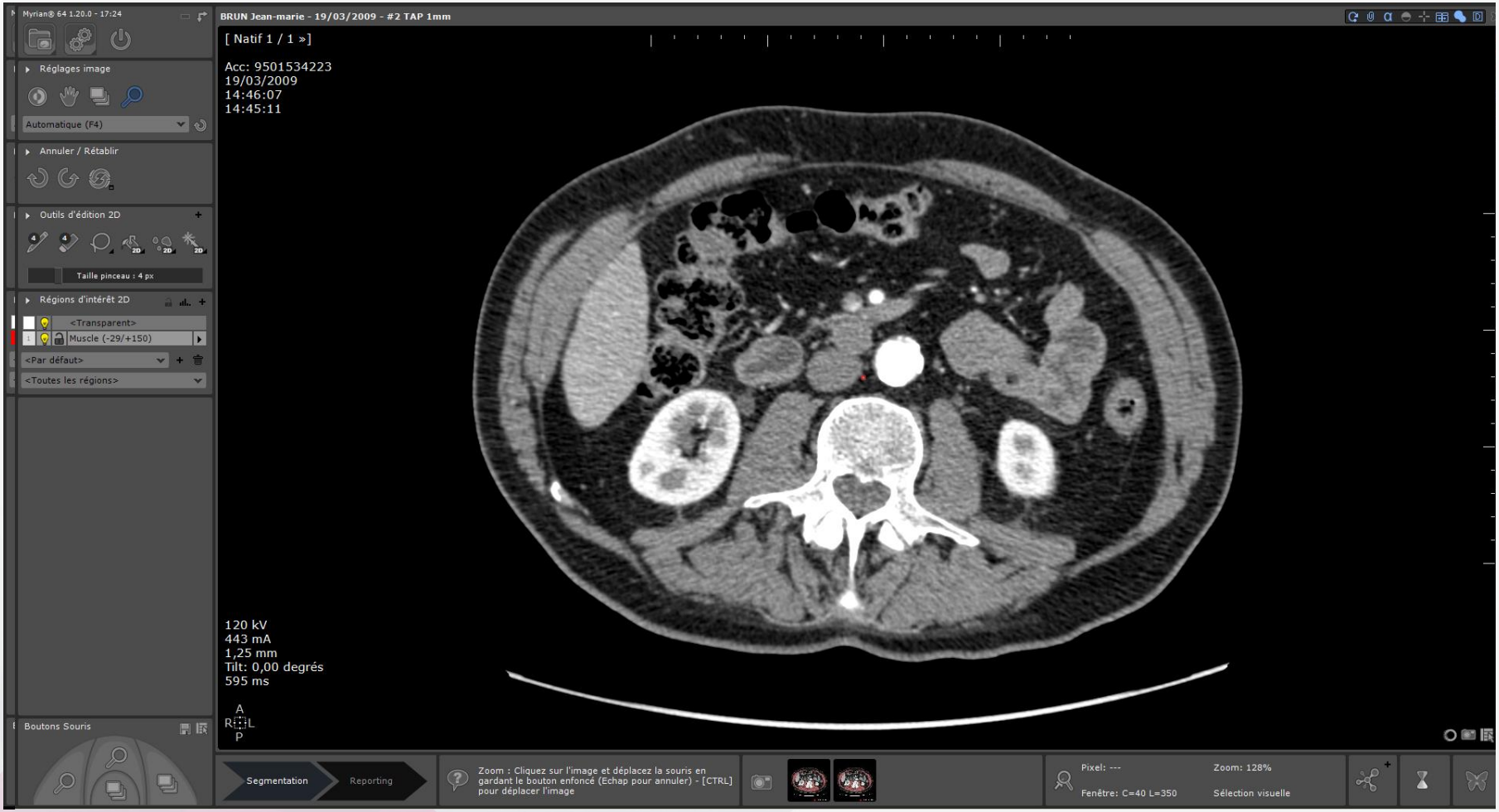
- CT scans for initial cancer staging were used to quantify skeletal muscle area.
- Third lumbar vertebra axial slices were selected for analysis.
- CT image parameters included: contrast or non contrast-enhanced, 5-mm slice thickness, 120 kVp, and ~290 mA.
- Skeletal muscles were semi automatically identified by software within a Hounsfield unit(HU) range of −29 to +150 HU.
- Surface obtained was than manually corrected by a radiologist

MATERIALS AND METHODS

Body composition measurements: two centers and softwares

Softwares	Centers	Radiologists
GOLD STANDARD SliceOmatic, TomoVision, Montreal, Quebec, Canada	Department of Oncology, University of Alberta, Edmonton, Canada	1 senior
DEDICATED SOFTWARE Myrian, Intrasense, Montpellier, France	Institut régional du Cancer de Montpellier (ICM), Montpellier, France	1 junior 1 senior

MYRIAN STEPS Loading



MYRIAN STEPS automatic thresholding

MYRIAN STEPS

Manual correction of cutaneous and sub cutaneous tissues

MYRIAN STEPS Manual correction of visceral tissues

MYRIAN STEPS Manual correction of L3 vertebrae

Informations patient

Poids:	74,0	kg
Taille:	172	cm
Sexe:	M	

Analyse de l'image

Surface de masse maigre L3:	14590	mm²
Surface de masse maigre L3:	146	cm²

Calcul de la dose d'Eloxatine (Seuil = 3.09 mg/kg)

Body Surface Area *:	1,87	m²
Lean Body Mass *:	49,8	kg
Dose Oxali (85mg/m² x BSA):	158,8	mg
(Dose Oxali BSA)/LBM:	3,19	mg/kg
Dose Oxali (3.09mg/kg x LBM):	154,0	mg
Validé par:	rt	

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Patient:

Patient ID: 0100336

Né(e) le: 07/04/1956

14/01/2016

Date scanner: 28/04/2011

Heure scanner: 115435

Protocole LEANOX: calcul de la dose d'eloxatine (version ALPHA)

Informations patient

Poids:	71,8 kg
Taille:	160 cm
Sexe:	F

Analyse de l'image

Surface de masse maigre L3:	104 cm²

Calcul de la dose d'Eloxatine (Seuil = 3.09 mg/kg)

Body Surface Area *:	1,75 m²
Lean Body Mass *:	37,1 kg
Dose Oxali (85mg/m² x BSA):	148,8 mg
(Dose Oxali BSA)/LBM:	*4,01 mg/kg*
Dose Oxali (3.09mg/kg x LBM):	114,7 mg
Validé par:	mt

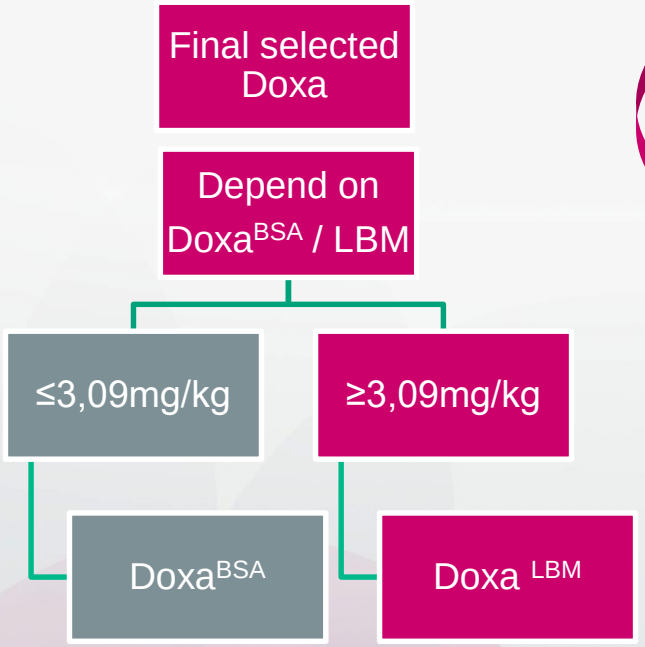
Groupe de randomisation:

Groupe A (85mg/m² x BSA)	☐
Groupe B (85mg/m² x BSA)	☐
Groupe C (3.09mg/kg x LBM)	☐

Dose Eloxatine (à renseigner par l'investigateur):

Signature Biostat:

Signature Médecin:



Matériel et méthode

- The doses of oxaliplatine calculated and chosen by every software and every operator, as well as the times of measure, are compared by the Wilcoxon test for mated data.
- The **K** coefficient was calculated to measure the concordance between softwares and operators.
- These analyses are led with the software STATA version 13.0.

	N	%	average	sd	median	range
height (cm)	101		168.2	7.9	168.0	[150.0 ; 188.0]
weight (kg)	101		67.8	14.5	65.0	[40.0 ; 107.0]
BMI (kg/m²)	101		24.0	5.1	23.0	[15.3 ; 40.3]
Thinness	10	9.9				
Normal	57	56.4				
overweight	24	23.8				
obesity	10	9.9				
BSA (cm²)	101		1.8	0.2	1.8	[1.3,2.2]
IV CM inj						
no	15	15				
Yes	86	85				
Oxaliplatine dose (mg)	101		149.9	15.8	148.8	[113.1;188.9]

Population characteristics

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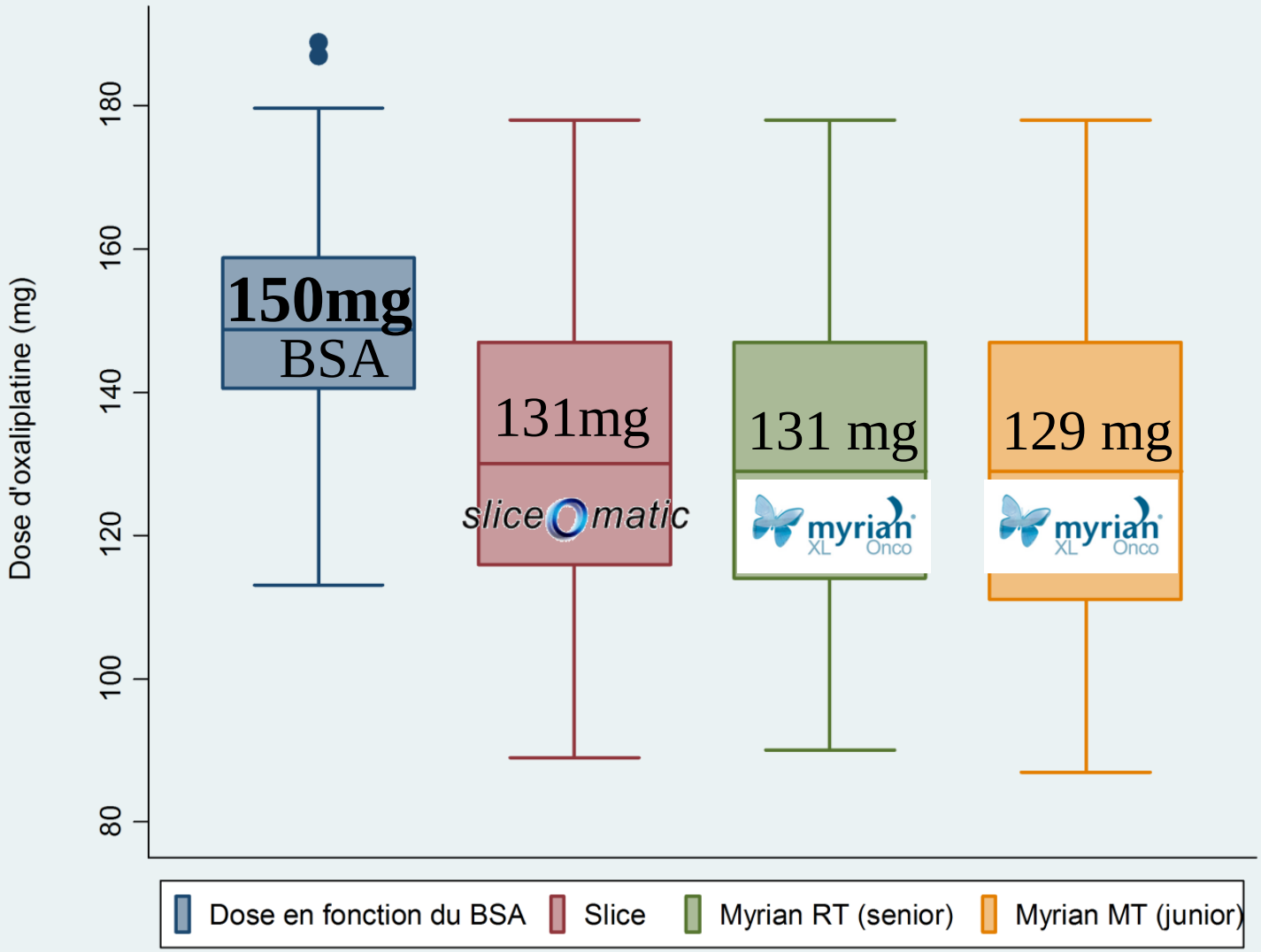
description of the parameters and of the dose chosen according to the software and the operators

	N	%	average	sd	median	range
Slice O Matic						
Lean Body Mass (kg)	101		43.2	8.1	42.1	[28.9 ; 64.8]
Dose oxali BSA / LBM (mg/kg)	101		3.5	0.6	3.5	[2.5 ; 5.4]
<3.09 (mg/kg)	21	20.8				
≥3.09 (mg/kg)	80	79.2				
Dose Oxali (3,09mg/kgxLBM) (mg)	101		133.6	25.0	130.0	[89.0 ; 200.0]
Choix Dose Oxali (mg)	101		131.0	21.4	130.0	[89.0 ; 178.0]
MYRIAN – MT (Junior)						
Time (s)	101		146.8	45.6	142.0	[60.0 ; 295.0]
Lean Body Mass (kg)	101		42.6	8.3	41.6	[28.2 ; 64.7]
Dose oxali BSA / LBM (mg/kg)	101		3.6	0.6	3.6	[2.5 ; 5.1]
<3.09 (mg/kg)	17	16.8				
≥3.09 (mg/kg)	84	83.2				
Dose Oxali (3,09mg/kgxLBM) (mg)	101		131.5	25.6	128.6	[87.0 ; 200.1]
Choix Dose Oxali (mg)	101		129.3	22.3	129.0	[87.0 ; 178.0]
MYRIAN – RT (Senior)						
Time (s)	101		123.0	52.6	113.0	[51.0 ; 400.0]
Lean Body Mass (kg)	101		43.0	8.0	41.8	[29.0 ; 63.7]
Dose oxali BSA / LBM (mg/kg)	101		3.6	0.5	3.5	[2.5 ; 5.1]
<3.09 (mg/kg)	20	19.8				
≥3.09 (mg/kg)	81	80.2				
Dose Oxali (3,09mg/kgxLBM) (mg)	101		132.8	24.6	129.2	[89.5 ; 196.7]
Choix Dose Oxali (mg)	101		130.5	21.3	129.0	[90.0 ; 178.0]

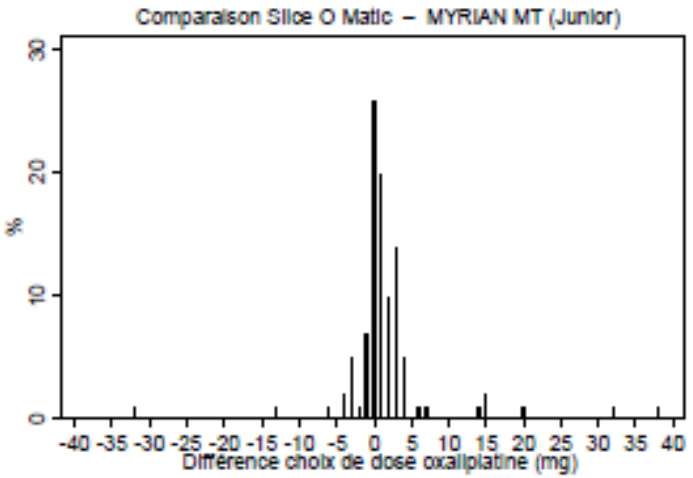


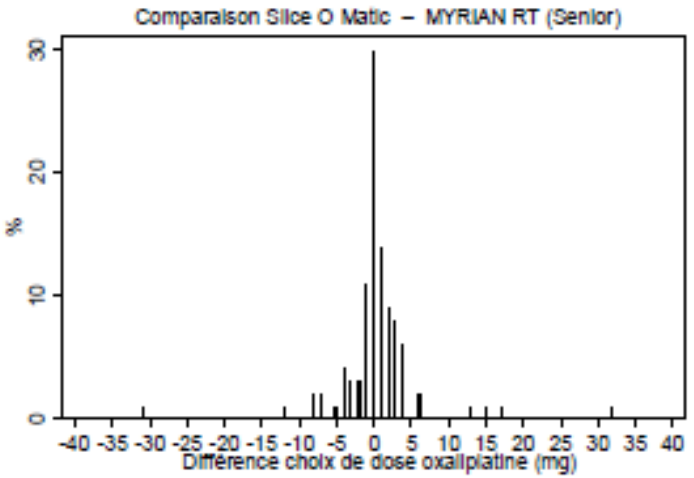
Comparison of oxaliplatin doses chosen by the operators compared with those calculated according to the BSA

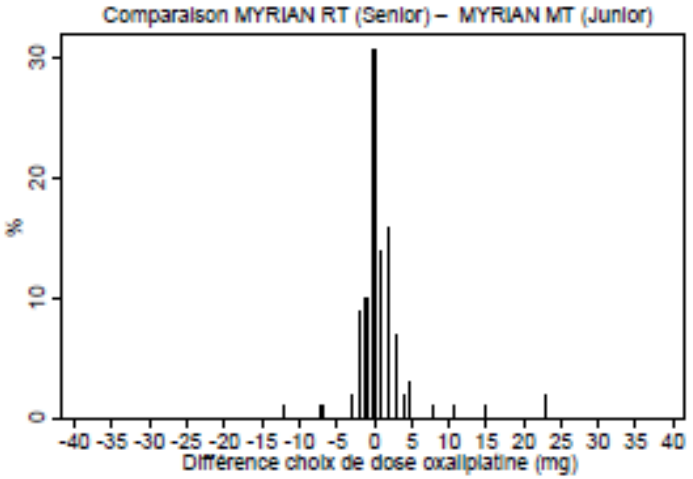
Comparison of the measurement times and of the dose chosen according to the software and the operators

	N	average	SD	median	range	IQR	p
Différence du choix de dose Oxali (mg)							
Slice O Matic – MYRIAN MT (Junior)	101	1.6	7.0	1.0	[-32 ; 38]	[0 ; 3]	<0.001
Slice O Matic – MYRIAN RT (Senior)	101	0.5	5.9	0	[-31 ; 32]	[-1 ; 2]	0.10
MYRIAN RT (Senior) - MT (Junior)	101	1.2	4.3	0	[-12 ; 23]	[0; 2]	0.002
Différence du temps de mesure (s)							
MYRIAN RT (Senior) – MT (Junior)	101	-23.7	54.0	-30.0	[-186 ; 235]	[-52 ; -1]	<0.001

*IQR= Interquartile Range







histogram of the difference of dose chosen between the operators

- The statistical analysis in subgroups (BMI, CM) does not modify the significance of the differences between the novice and the 2 other expert operators

- Removal of the 10 more problematic cases (due to oedema in subcutaneous fat) does not modify the significance of the differences between the novice and the 2 other expert operators

- Proportion of patients diagnosed with sarcopenia:
  - ✓ Canadian expert center withSlicomatic = 79.2%,
  - ✓ French junior with Myrian = 83,2%
  - ✓ french senior with Myrian = 80.2%.
- The concordance between software and operators for the determination of the sarcopenia status is almost perfect (κ> 0.81).

- We validated a software dedicated to the calculation and to the choice of the dose of oxaliplatin use as adjuvant chemotherapy in CRC;
- It tooks into account the eventuality of a sarcopeny at risk of greater neurotoxicity, determined on the basis of the baseline CT-scan
- Between expert hands, this solution makes as well as the goldstandard, in record time.

To follow

Project title
LEANOX LEAn body mass Normalization of OXaliplatin based chemotherapy for stage III colorectal patients treated in adjuvant setting : Impact on oxaliplatin induced sensitive neurotoxicity. A Multicenter Phase II Randomized trial.