

The Proteus project

Colon Rectal Cancer Screening by using CT Colonography



The Proteus project

Randomized trial comparing participation and detection rate of CTC vs. FS for CRC screening.

- ✓ 26,000 invitations by letters
- ✓ 10 centers performing CTC scanning (8 in Piedmont, 2 in Verona)
- ✓ CTC scans sent to the screening center for reporting
- ✓ CTC reading assisted by CAD (Computer Aided Detection)

Lo studio Proteus

- Telediagnosis makes the method widespread and available locally
- A board of experienced radiologist guarantees high diagnostic standards



Rational of using CAD

- ✓ Long reporting times for unassisted reading (10-20 minutes): higher costs
- ✓ CAD may reduce inter-observer variability
- ✓ CAD may reduce interpretation errors: 20% of the patients with polyps ≥ 6 mm are not detected by CTC

CAD reading paradigm

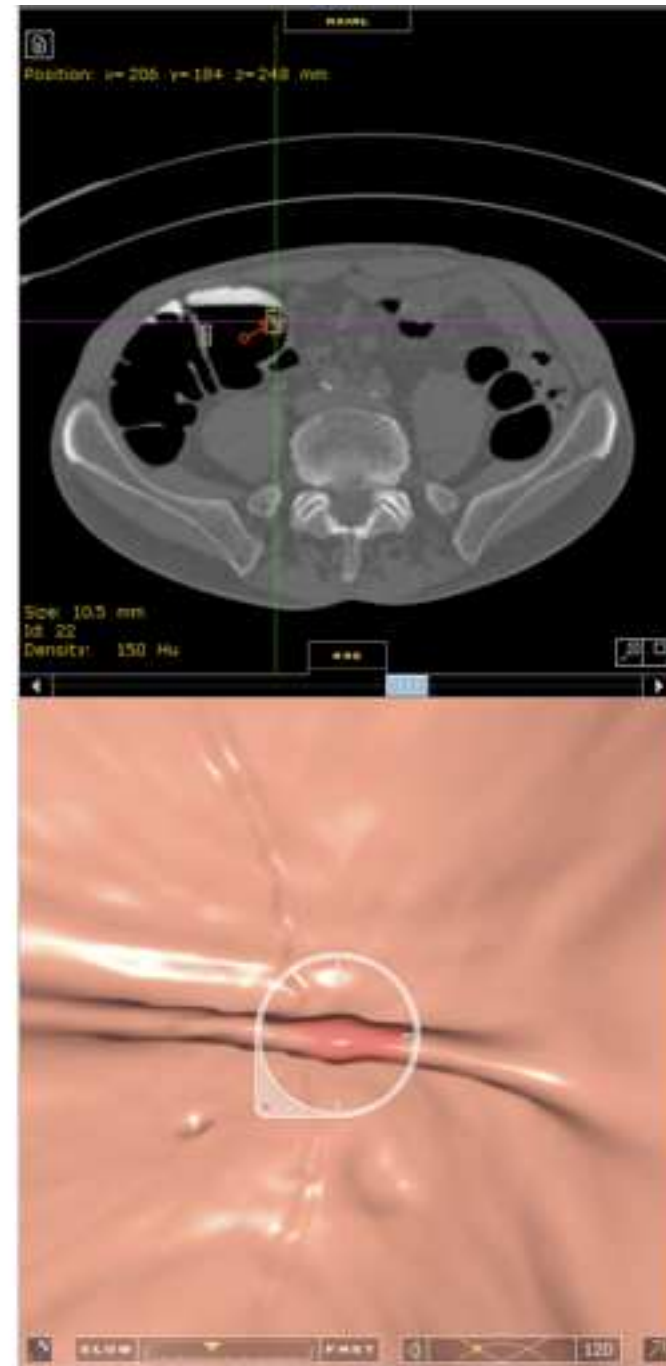
- ✓ **Second Reader CAD:** (CAD applied only after unassisted evaluation) is the classic paradigm used in most prior research. However, such implementation increases interpretation time.
- ✓ **Double reading with CAD as First reader (DR-FR):** CAD as first reader followed by a fast unassisted 2D review to identify large and atypical lesion

1° READER

TYPE	DISTANCE	CORRECTOR
P	5.4	23.0
C	27.6	7.9
C	45.7	3.0
C	102	5.0
C	130	0.6
C	155	0.0
C	155	3.3
C	160	10.5
C	161	9.9
C	162	11.2



2-4 min



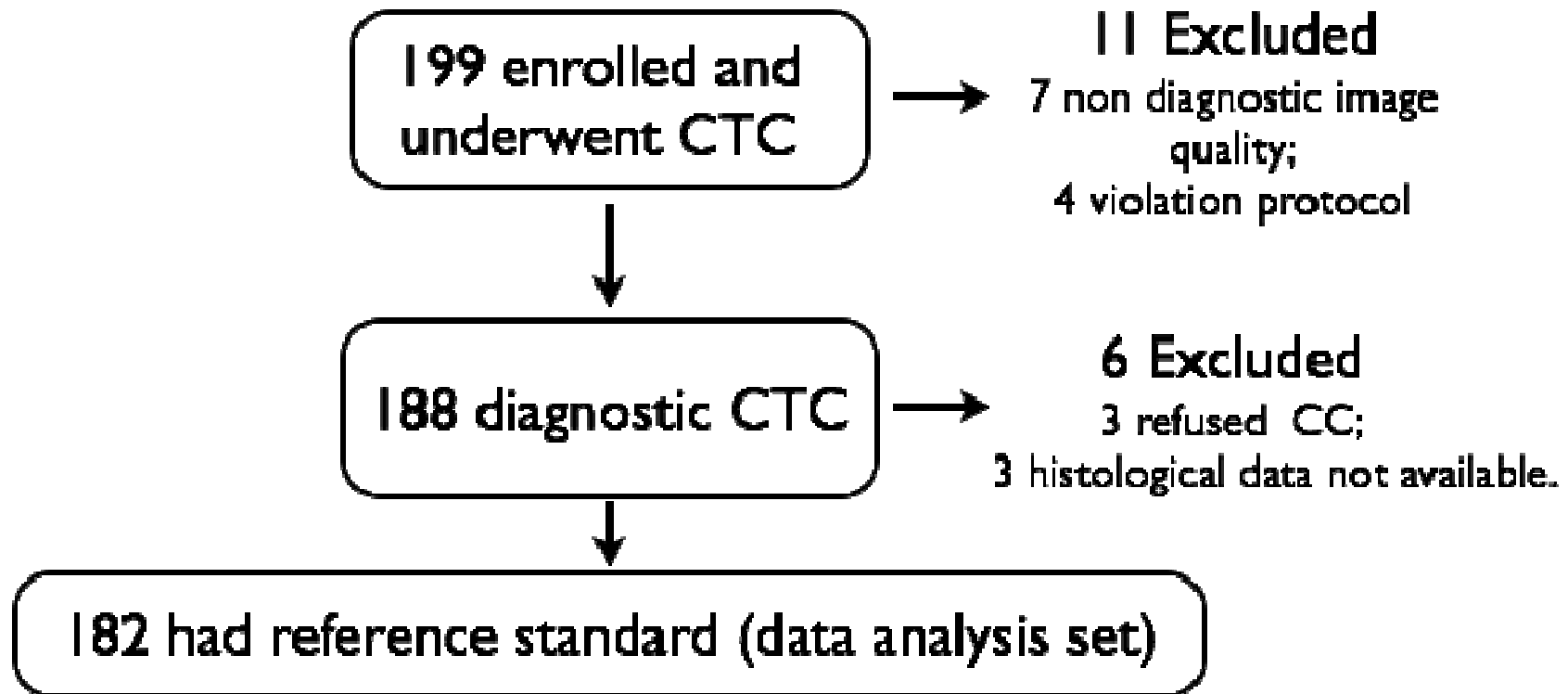
Rationale of using DR FR CAD

- The idea of using FR CAD may be feasible today, now that CAD systems have a stand-alone per polyp sensitivity of more than 90% time.
- DR FR CAD diagnostic performance CAD and reader-CAD interaction are largely unknown in a screening setting.

Proteus: Preliminary studies

- Two preliminary studies measuring diagnostic performance and time efficiency of DR FR CAD:
 - A retrospective study comparing observer variability of DR FR CAD with unassisted reading (155 cases; 57 with polyps 6 mm or larger)
 - A prospective study in patients FOBT+ comparing diagnostic performance and time efficiency of DR FR vs. SR CAD (199 enrolled patients).

Double Reading with CAD first reader vs. Second reader CAD



89 Negative

- 58 No Lesion
- 6 Advanced adenoma ≤ 5 mm
- 17 Low risk adenoma ≤ 5
- 8 Non-adenomatous lesions

93 Positive (cancer or adenoma ≥ 6 mm)

- 13 Cancer ≥ 10 mm
- 48 Advanced adenoma ≥ 10 mm
- 15 Advanced adenoma 6-9 mm
- 17 Low risk adenoma 6-9 mm

Double Reading with CAD first reader vs. Second reader CAD

Reading Paradigm

	Second Reader		Double Reading FR	
	Radiologist	Radiologist + CAD	FR CAD	CAD+ Radiologist
Sensitivity (%)	80 (74/93) (70,87)	86 (80/93) (77,92)	85 (79/93) (75,91)	89 (83/93) (81,95)
Specificity (%)	92 (82/93) (82,97)	90 (80/89) (82,95)	93 (83/93) (86,97)	91 (81/93) (83,96)
PPV (%)	91 (74/81) (83,96)	90 (80/89) (82,95)	92 (78/84) (85,97)	91 (83/91) (83,96)
AUC	0.86 ± 0.04	0.90 ± 0.03	0.92 ± 0.02	0.94 ± 0.02

The difference in sensitivity between SR and DR with FR CAD was not statistically significant (P=0.5)
 Compared to the Unassisted reading, CAD increased sensitivity for both reading paradigm (P=0.03)
 For both CAD reading modes, the AUCs increased with CAD (P=0.02)

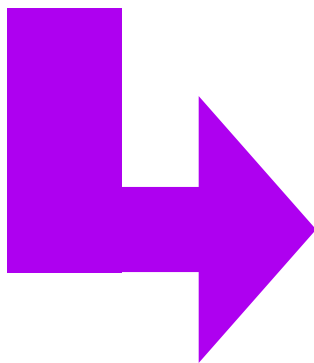
Double Reading with CAD first reader vs. Second reader CAD

Reading Paradigm	Interpretation Time		
	Phase 1	Phase II	TOT
Second Reader CAD	318 ± 27 sec	177 ± 20 sec	495 ± 38 sec
First Reader CAD + 2D review	276 ± 20 sec	108 ± 8 sec	384 ± 22 sec

Double reading with FR CAD reporting time was significantly shorter than the SR CAD (p=0.001)

Double reading with CAD as first reader

- Use of CAD significantly improves per-patient and per polyp detection, without a clinically unacceptable decrease in specificity.
- Double reading with FR CAD is more time efficient and has similar diagnostic performance to Second Reader CAD.



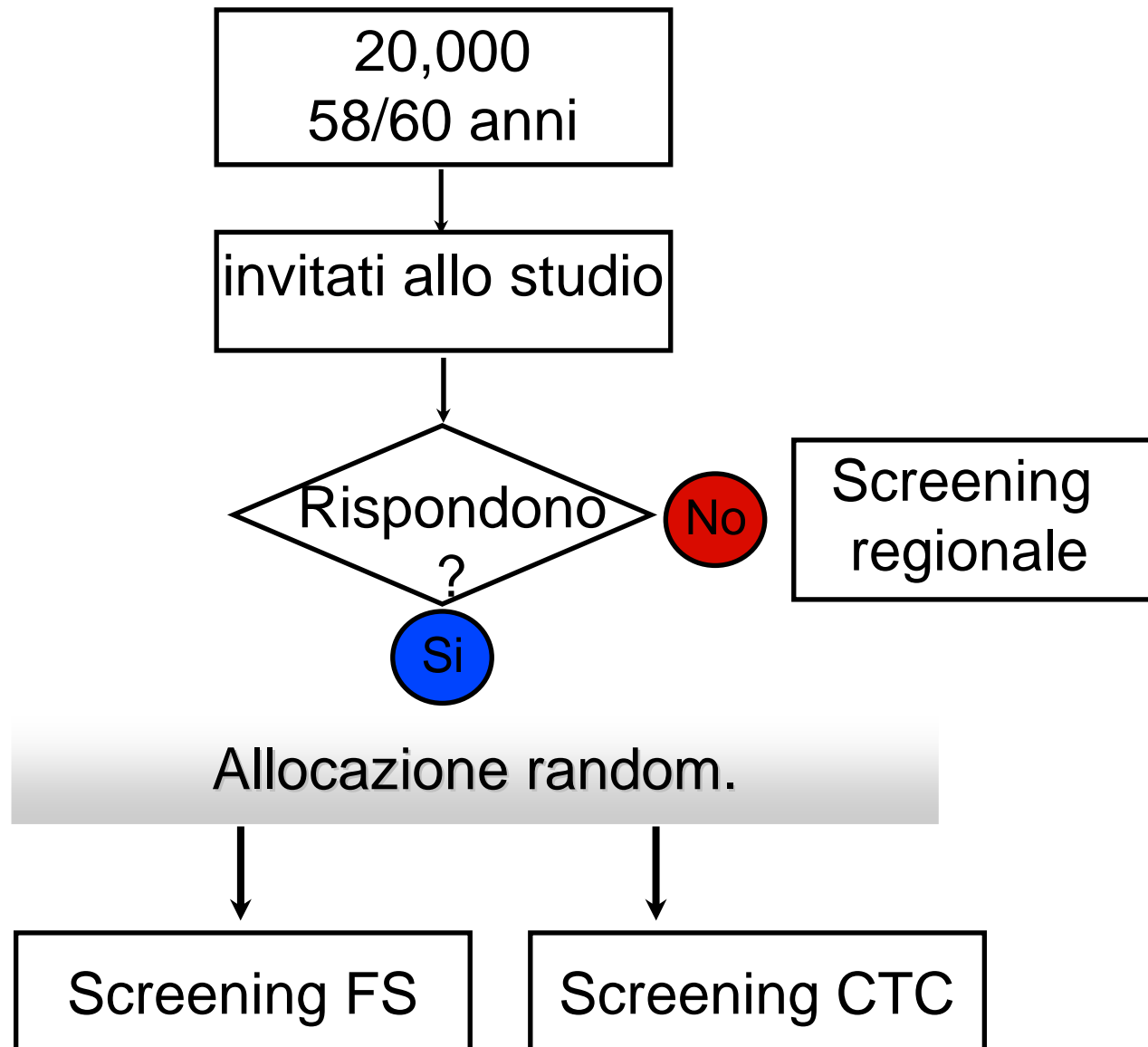
Double reading with FR CAD should be considered for future mass screening program, where cost-effectiveness may represent a key issue

Training for CTC interpretation in a screening setting

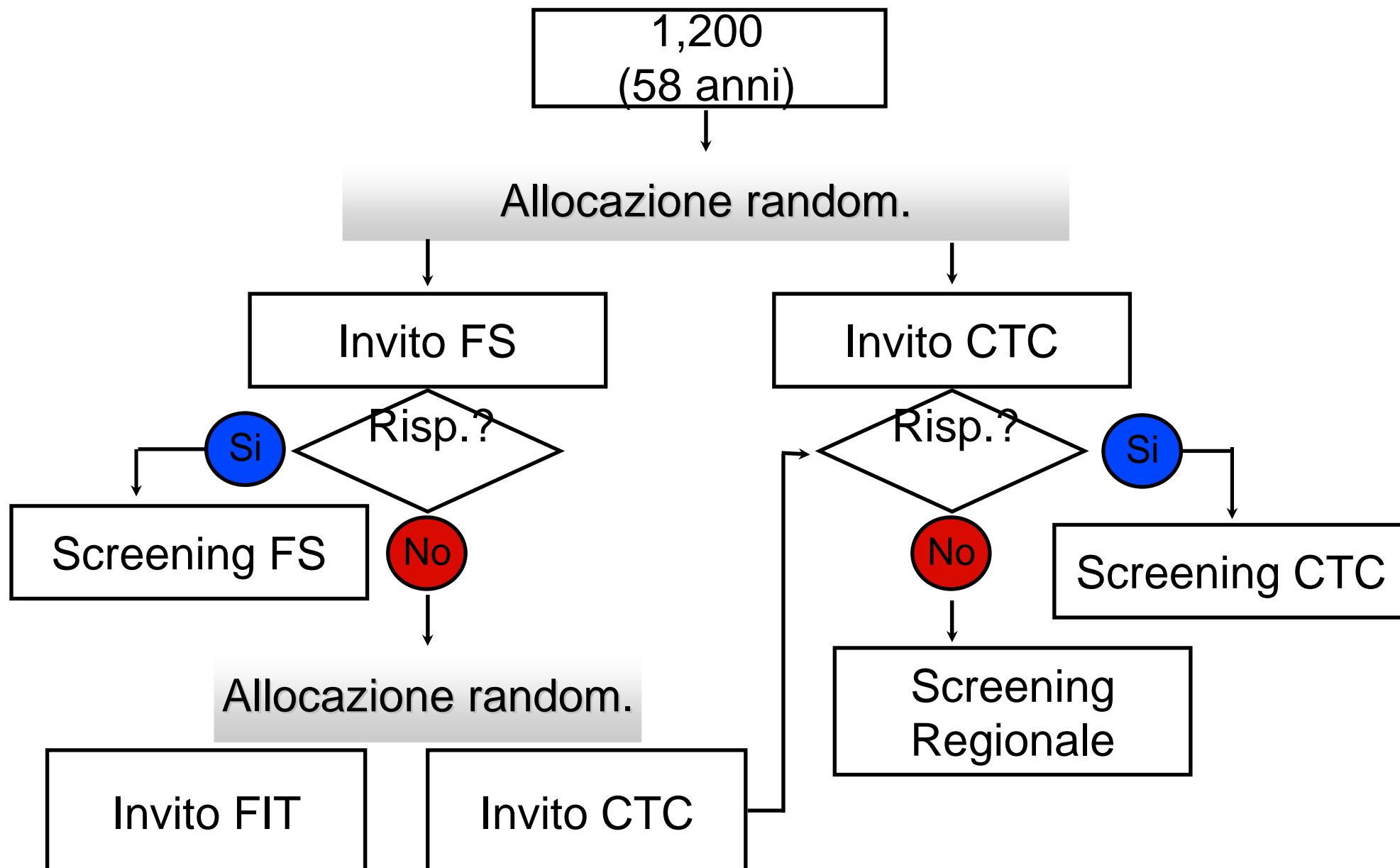
- CTC is a relatively hard technique to learn
- So far, no consensus exists about the level of experience needed for accurate CTC screening

12 radiologists participated in a 2-day educational course in CTC. Subsequently, radiologists took a qualification examination composed of 30 CTC cases (14 cases with a total of 24 polyps 6 mm or larger).

Proteus detection rate



Proteus participation



Inclusion/exclusion criteria

Inclusion

Asymptomatic and average risk for CRC

Exclusion

- Prior polyp surveillance
- CC and/or FOBT with the past 2 years
- History of bowel disorder (IBD, polyposis syndromes)
- Lack of capacity to give informed consent

Sample size

Proteus detection rate

We anticipated a participation rate of 25% in the study. Including 20,000 participants in the trial we will then achieve a power of 80% to detect a difference of 2% in detection rate of advanced neoplasia between the two screening arms with a significance of 0.05

Proteus participation rate

We anticipated a participation rate of 25% in the FS arm. Including 1200 participants in the trial we will then achieve power of 80% to reject the null hypothesis of no differences with a significance of 0.05

Adesione

FS	Novembre	Gennaio	Febbraio	Marzo	Aprile	Luglio	TOTALE	Settembre
Invitati	568	465	464	231	1275	543	3546	621
Aderenti	54	42	44	18	137	57	352	47
	9,5%	9,0%	9,5%	7,8%	10,7%	10,5%	9,9%	7,6%
Rifiutano	16	13	12	5	35	10	91	4
	2,8%	2,8%	2,6%	2,2%	2,7%	1,8%	2,6%	0,6%

CTC	Novembre	Gennaio	Febbraio	Marzo	Aprile	Luglio	TOTALE	Settembre
Invitati	191	151	264	231	1276	543	2656	627
Aderenti	22	18	34	20	128	63	285	27
	11,5%	11,9%	12,9%	8,7%	10,0%	11,6%	10,7%	4,3%
Rifiutano	6	7	8	3	49	6	79	5
	3,1%	4,6%	3,0%	1,3%	3,8%	1,1%	3,0%	0,8%

Adesione

FS	UOMINI	DONNE	TOTALE
Invitati	1645	1905	3550
Aderenti	192	164	356
	11,7%	8,6%	10,0%
Rifiutano	45	46	91
	2,7%	2,4%	2,6%

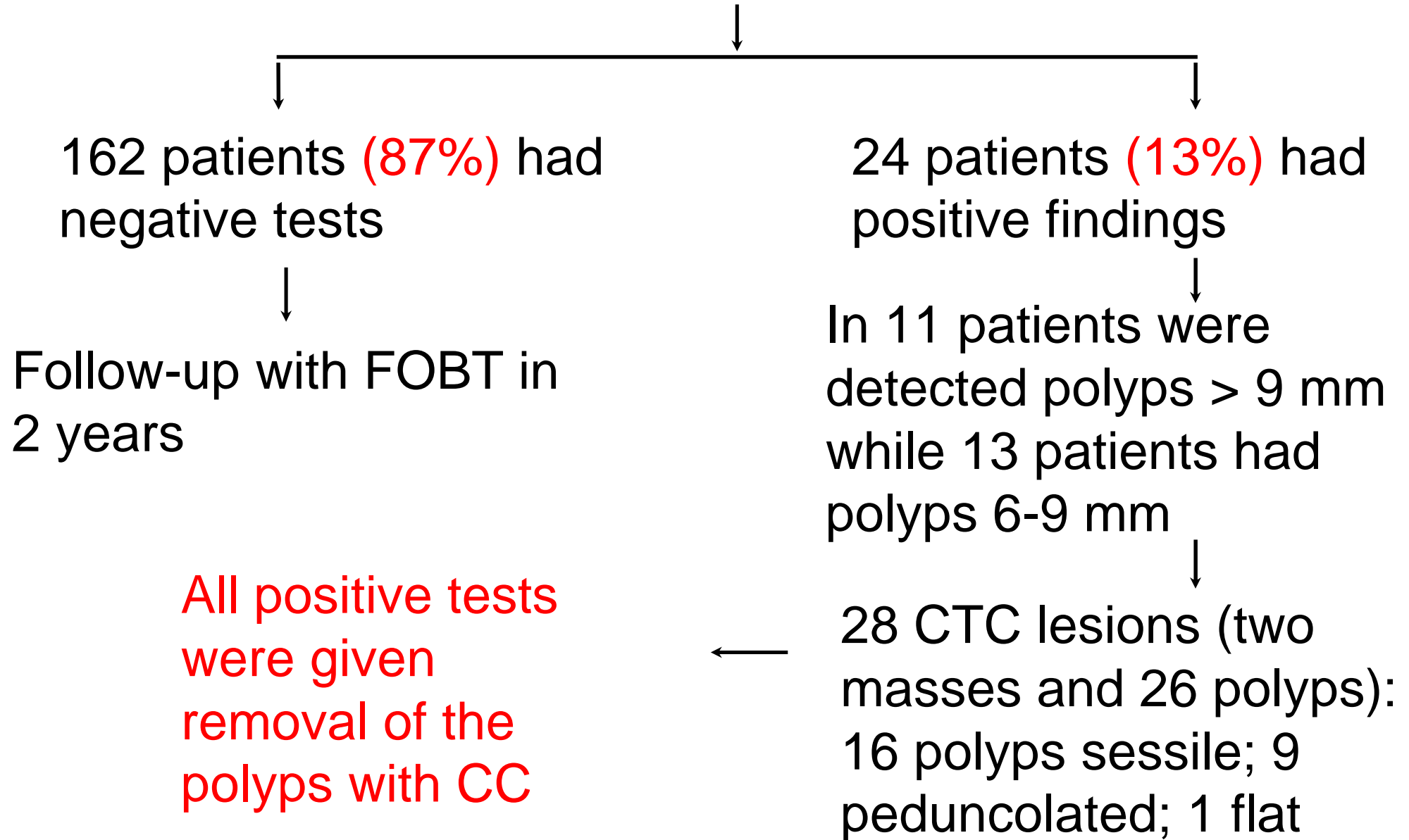
CTC	UOMINI	DONNE	TOTALE
Invitati	1233	1423	2656
Aderenti	150	135	285
	12,2%	9,5%	10,7%
Rifiutano	33	46	79
	2,7%	3,2%	3,0%

Detection rate: preliminary results

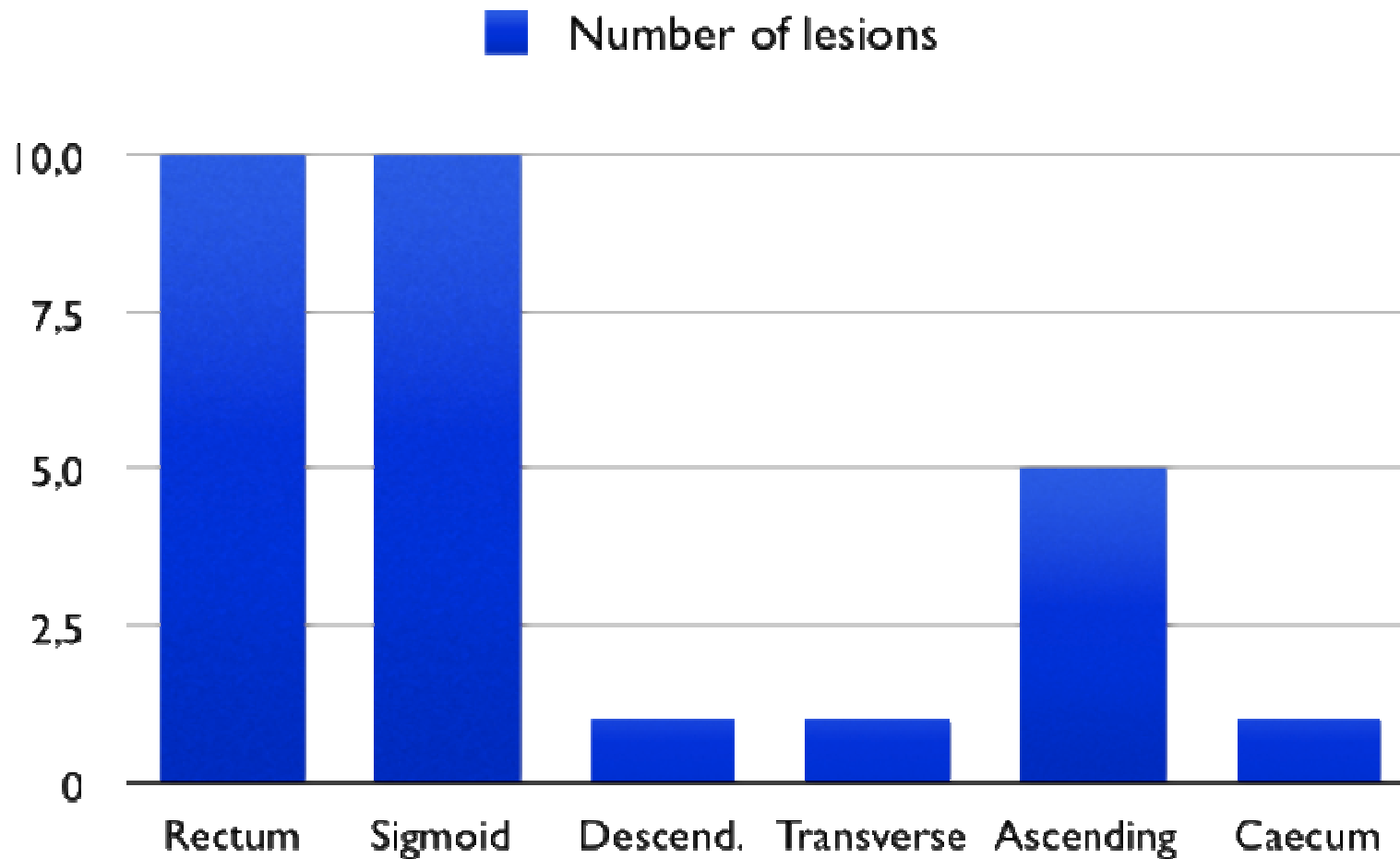
- A total of 186 subjects (97 males) were enrolled in the CTC arm (July 2011).
- All patients underwent CTC after limited bowel preparation consisting of a regime of meal-time mild laxative, followed by iodine administered 2h before CTC scan (same-day preparation)

Detection rate: preliminary results

186 Patients were enrolled in CTC screening



CTC findings characteristics



CTC screening costs

- Non diagnostic examinations occurred in 4 patients (2%).
- Mean interpretation time for analyzing CAD output was 177 seconds (74, 234); the mean additional time for unassisted review was 82 seconds (46,100)
- Incidental extra-colonic findings were observed in 14 patients; diagnostic imaging exams were recommended only in 2 patients (1% potentially important findings).

Conclusion

- Quality metrics for CTC (bowel preparation, training/experience, reader-CAD interaction, standard-documentation of clinically relevant colonic and extra-colonic lesions) were measured in the preliminary studies of the Proteus project to facilitate quality implementation of CTC.
- Preliminary studies indicate that the use of CAD reduces interpretation times without significantly affects specificity, thus allowing improved work flow efficiency in the screening environment.
- It is needs to understand causes of the low participation in the trial (subjects characteristics; experimental procedure)

Proteus: Qualification examination

- ✓ CAD detected 88% (21/24) of the polyps with a false-positive rate of 11 FP/scan
- ✓ Individual reader per-patient sensitivity ranged from 29% to 100% (mean per-patient sensitivity: 75%)
- ✓ Mean specificity was 92% (range, 75-100%)
- ✓ Across all readers AUC went from 0.79 to 0.98

Qualification examinations

- The level of experience affects the accuracy and time-efficiency of CTC.
- CAD cannot substitute reader experience
- Structured training does not reduce the performance gap between the experienced and inexperienced readers.