PCLS 抄読会

2021/9/22

弘前大学腫瘍内科
青森新都市病院　総合診療科
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  →弘前大学腫瘍内科
  → 青森新都市病院
- プライマリ・ケア認定指導医
  認定内科医　病院総合診療学会認定医
  外科専門医　消化器内視鏡専門医
  緩和医療学会認定指導医 ほか

はじめに

- 本日お話させていただく内容は、本邦での大腸がん治療ガイドラインから大きく逸脱したものです。よって、目の前の患者さんに外挿するか否かは本人の希望はもとより、地域の事情や連携医療機関の外科医・腫瘍内科医・放射線科医とよく相談してください。
- お話する内容をそのまま行ったとしても結果は保証されていません。研究会や勉強会で同じ内容をお話する際は個人の責任でお願いします。

本日の内容

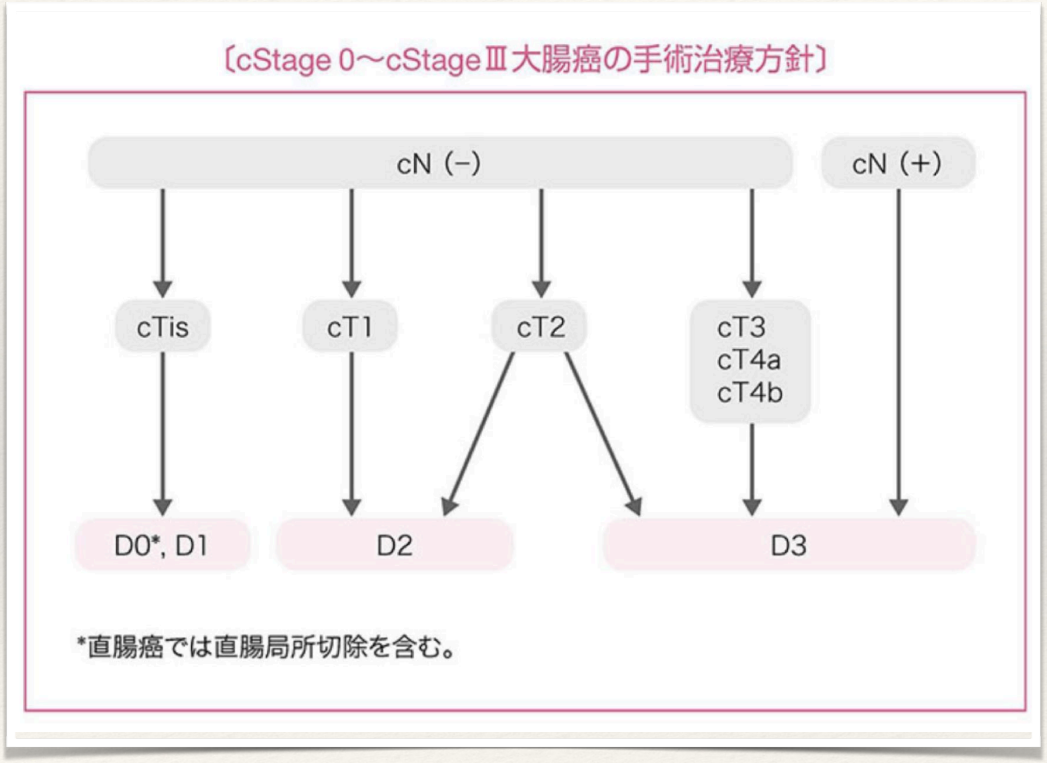
- 局所進行直腸がんに対する非切除治療(放射線化学療法)

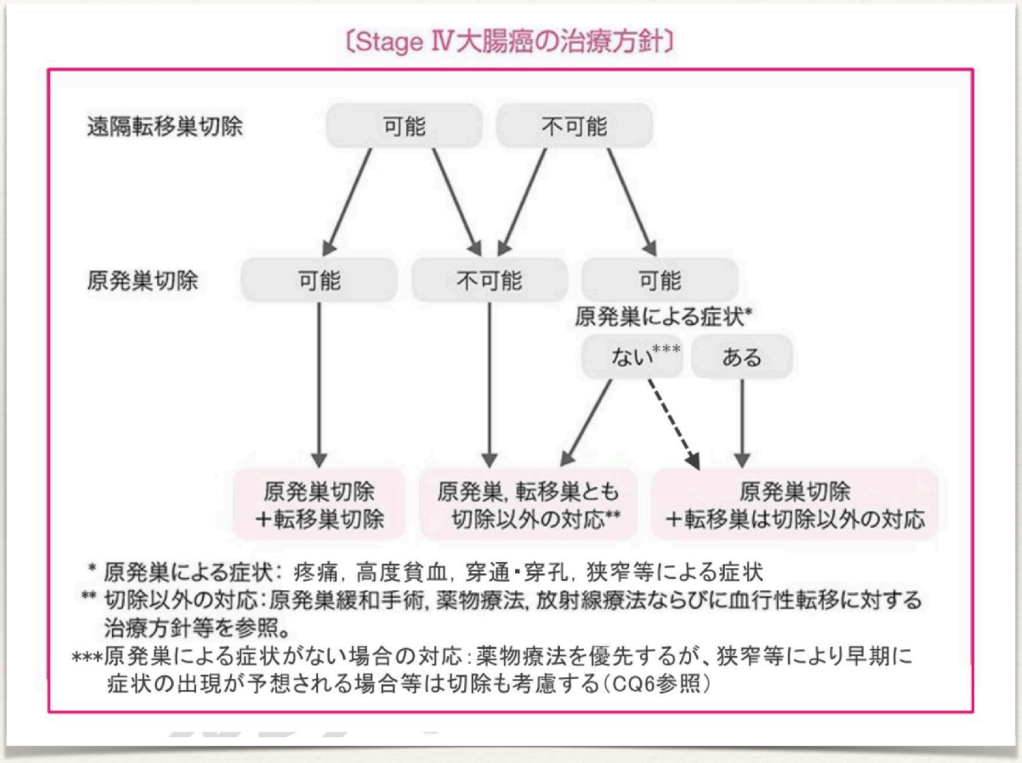
  The watch-and-wait strategy versus surgical resection for rectal cancer patients with a clinical complete response after neoadjuvant chemoradiotherapy

- 局所進行直腸がんに対する術前化学療法としてのFOLFIRINOX療法

  Neoadjuvant chemotherapy with FOLFIRINOX (UNICANCER-PRODIGE23)

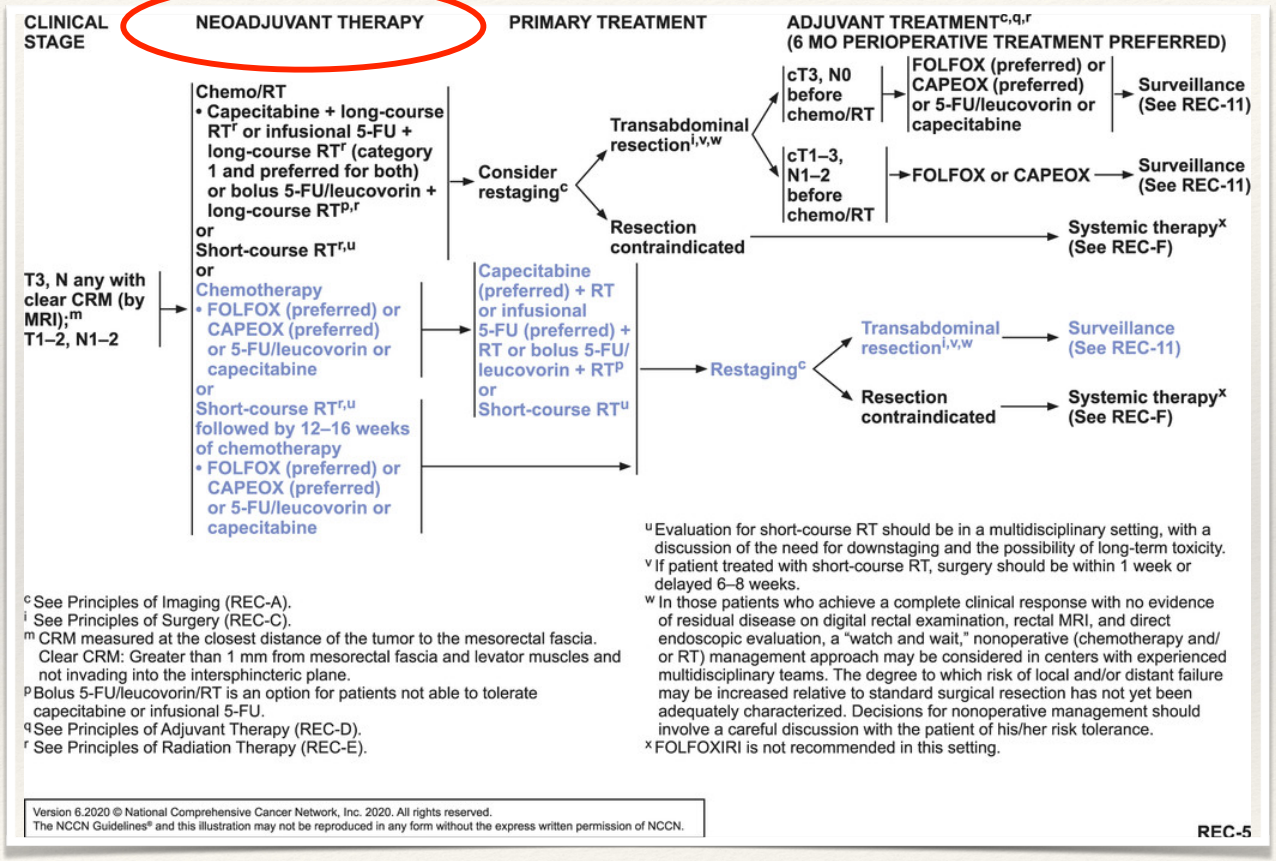
日本の大腸がん診療





基本は手術による切除 ± 補助化学療法

NCCNガイドライン2020



直腸がん手術は負担が大きい

【術後合併症】

1. 肛門機能障害　神経温存TME手術
2. 排尿機能障害　性腺機能障害
3. 性腺機能障害　排尿機能障害が60%
4. **人工肛門造設**

83%の患者が術前化学放射線療法による治療を希望し、94%の患者さんが2年後に25%の再発率でも受け入れ、20%の遠隔転移でも受容すると回答した

TME:Total Mesorectal Excision,
全直腸間膜切除

- Gani C, Gani N, Zschaeck S, et al. Organ Preservation in Rectal Cancer: The Patients' Perspective. Front Oncol 2019;9:318.
- Gunjur A, Chazan G, Newnham G, et al. Pilot study of patients' preferences for immediate resection versus a watch and wait approach after neoadjuvant chemoradiation for locally advanced rectal cancer. JCO Oncol Pract 2020;17(2):e149–57.

私の考え方&立場

- 不要な手術はするべきではない

  「精緻で”過剰な侵襲”は外科医の自己満足」「手術は”絶対的正義”ではない」

- 入浴、温泉が余暇の過ごし方として充実している日本では

  人工肛門は”仮に予防的なものであっても”極力、避けるべきである

- 高齢男性であっても性腺機能障害は避けるべきである

➡ 手術回避をとても好意的に考えるフィルター有り

直腸がんのWatch and Wait (WW)

日本大腸肛門病会誌　73：433-441，2020

特集　主題Ⅰ：大腸癌術前治療 up-to-date

Ⅵ．直腸癌術前化学放射線療法：Watch and Wait の up-to-date

小西　　毅
Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center

近年，直腸癌に対する術前化学放射線療法，さらに術前全身化学療法を加えるレジメンの開発により，病理学的完全奏効に至る症例が増えている．このような症例にも手術は標準治療して施行されてきたが，高率な合併症やストマ，さらに排便障害をはじめとする後遺症により，患者の QOL は著しく低下する．近年，術前治療後に臨床的完全奏効が得られた症例に対し，早急な手術を回避し経過観察する Watch and Wait 療法が提唱され，欧米を中心に安全かつ QOL の高い有効な治療法として注目されている．手術を前提としてきたこれまでの概念を大きく変える治療法であり，本邦においても正しい知識の普及と，適切な臨床導入が求められる．本項では直腸癌に対する Watch and Wait 療法の適応や成績，今後の展開について解説する．

索引用語：直腸癌，術前化学放射線療法，Watch & Wait，非手術療法，臓器温存

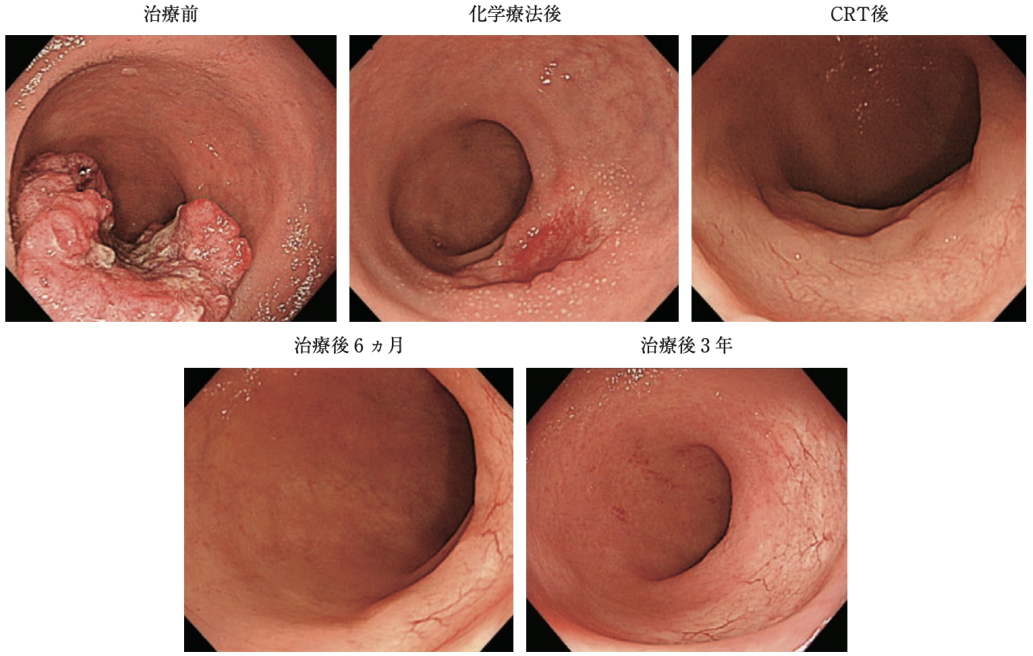
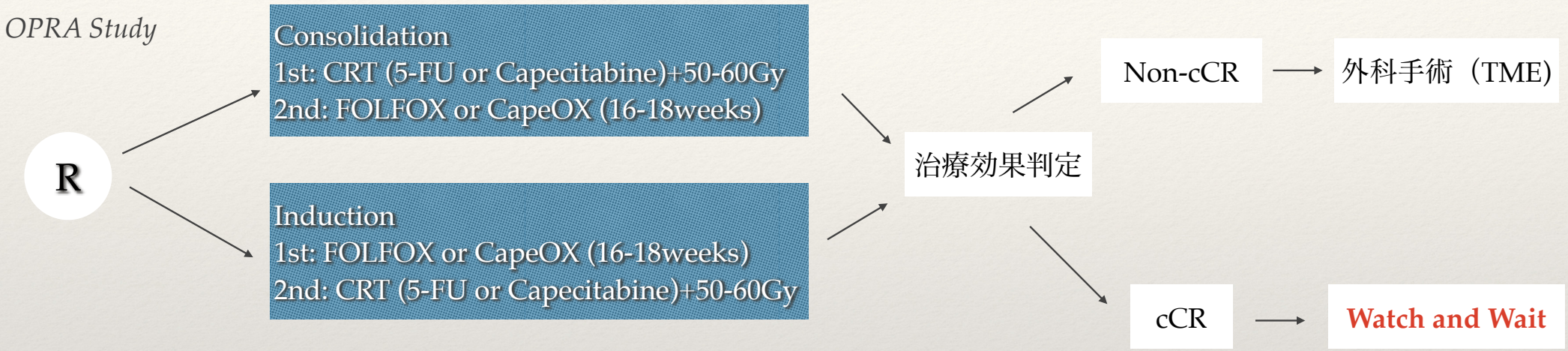


図 1　Watch & Wait 療法を行った 1 例（自験例）
63 歳　男性　T3 N3 (lt 263d) P0 H0 M0 c-stage Ⅲb
FOLFOX + BEV 6 コース → CRT 50.4Gy → 3 年間無再発

Watch and Wait Strategy by OPRA



	Induction	95%CI	Consolidation	95%CI	P
3年disease free survival	78%	(70%,87%)	77%	(69%,86%)	0.90
3年無遠隔転移生存率	81%	(74%,90%)	83%	(76%,91%)	0.86
3年TME-free survival	43%	(35%,54%)	58%	(49%,69%)	0.01

中国の孫逸山大学Cancer Centerからの発表

日本ではほとんど馴染みのない

「Watch and wait(WW)」の報告です

P: StageII/IIIの”切除可能”進行直腸がん患者

I: 術前化学放射線療法を受けて臨床的
　完全奏効(cCR)が得られた

C: TME手術でR0(腫瘍完全切除)を得た患者

O: Primary Disease Specific Survival(DSS)
　Secondary
　Non-regrowth 無局所再発生存期間(LRFS)
　Non-regrowth 無遠隔転移生存期間(DMFS)
　Disease Free survival, Overall survival,

RESEARCH Open Access

The watch-and-wait strategy versus surgical resection for rectal cancer patients with a clinical complete response after neoadjuvant chemoradiotherapy

Qiao-xuan Wang[1†], Rong Zhang[2†], Wei-wei Xiao[1†], Shu Zhang[1†], Ming-biao Wei[3], Yong-heng Li[4], Hui Chang[1], Wei-hao Xie[1], Li-ren Li[5], Pei-rong Ding[5], Gong Chen[5], Zhi-fan Zeng[1], Wei-hu Wang[4†], Xiang-bo Wan[3†] and Yuan-hong Gao[1*†]

Abstract

Background: The watch-and-wait strategy offers a non-invasive therapeutic alternative for rectal cancer patients who have achieved a clinical complete response (cCR) after chemoradiotherapy. This study aimed to investigate the long-term clinical outcomes of this strategy in comparation to surgical resection.

Methods: Stage II/III rectal adenocarcinoma patients who received neoadjuvant chemoradiotherapy and achieved a cCR were selected from the databases of three centers. cCR was evaluated by findings from digital rectal examination, colonoscopy, and radiographic images. Patients in whom the watch-and-wait strategy was adopted were matched with patients who underwent radical resection through 1:1 propensity score matching analyses. Survival was calculated and compared in the two groups using the Kaplan–Meier method with the log rank test.

Results: A total of 117 patients in whom the watch-and-wait strategy was adopted were matched with 354 patients who underwent radical resection. After matching, there were 94 patients in each group, and no significant differences in term of age, sex, T stage, N stage or tumor location were observed between the two groups. The median follow-up time was 38.2 months. Patients in whom the watch-and-wait strategy was adopted exhibited a higher rate of local recurrences (14.9% vs. 1.1%), but most (85.7%) were salvageable. Three-year non-regrowth local recurrence-free survival was comparable between the two groups (98% vs. 98%, $P=0.506$), but the watch-and-wait group presented an obvious advantage in terms of sphincter preservation, especially in patients with a tumor located within 3 cm of the anal verge (89.7% vs. 41.2%, $P<0.001$). Three-year distant metastasis-free survival (88% in the watch-and-wait group vs. 89% in the surgical group, $P=0.874$), 3-year disease-specific survival (99% vs. 96%, $P=0.643$) and overall survival (99%

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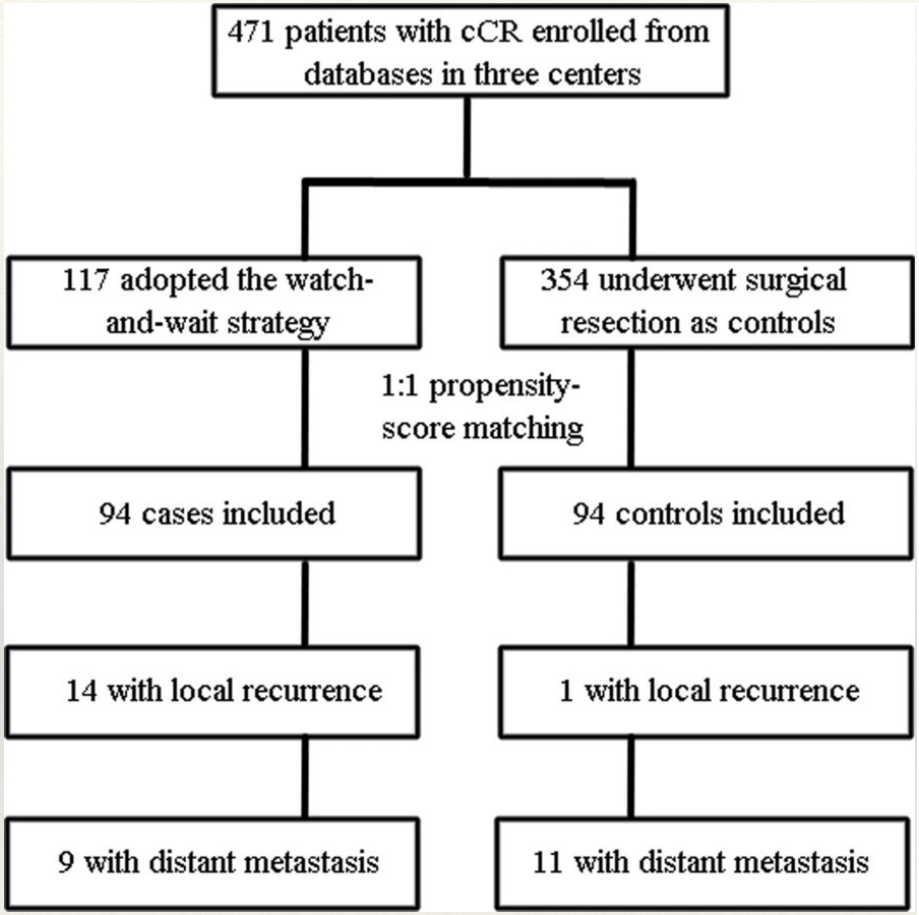


Table 1 Characteristics of patients according to treatment group (matched cohort)

	Surgical group (*N* = 94)	Watch-and-wait group (*N* = 94)	*P*
Age-median (IQR), year	56.0 (49.0–62.3)	57.5 (46.0–65.0)	0.760[b]
Sex			
Male	51 (54.3%)	55 (58.5%)	0.556[a]
Female	43 (45.7%)	39 (41.5%)	
WHO performance status-*N* (%)			0.665[a]
0	54 (57.4%)	49 (52.1%)	
1	39 (41.5%)	43 (45.7%)	
2	1 (1.1%)	2 (2.1%)	
T stage-*N* (%)			0.883[a]
T2	8 (8.5%)	9 (9.6%)	
T3	71 (75.5%)	68 (72.3%)	
T4	15 (16.0%)	17 (18.1%)	
N stage-*N* (%)			0.385[a]
N0	24 (25.5%)	19 (20.2%)	
N1/2	70 (74.5%)	75 (79.8%)	
Distance from anal verge-median (IQR), cm	4.0 (3.0–5.0)	4.0 (3.0–5.0)	0.996[b]
CEA-median (IQR), ng/ml	2.86 (1.71–4.77)	2.82 (1.61–4.74)	0.770[b]
Radiation dose, median (IQR), Gy	50 (50–50)	50 (50–50)	0.686[b]
Chemotherapy regimen-*N* (%)			0.875[a]
Capecitabine or fluorouracil only	29 (30.9%)	30 (31.9%)	
Capecitabine or fluorouracil plus oxaliplatin	65 (69.1%)	64 (68.1%)	
Therapeutic patterns in the neoadjuvant setting-*N* (%)			
Concurrent chemoradiotherapy only	21 (22.3%)	26 (27.7%)	0.501[a]
Concurrent chemoradiotherapy plus induction and/or consolidation chemotherapy	73 (77.7%)	68 (72.3%)	

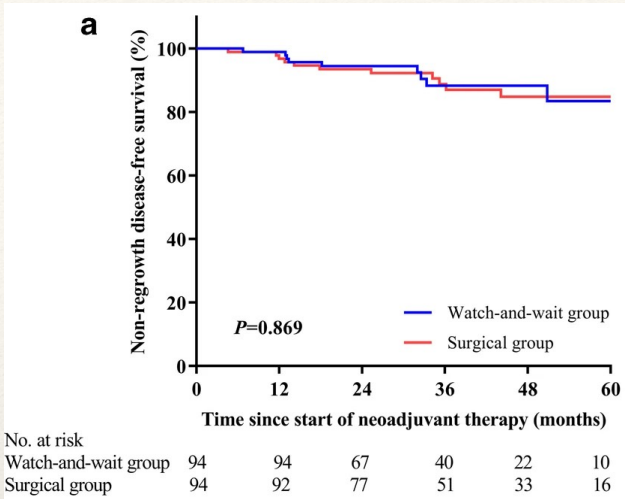
Data are showed in *N* (%) or median (interquartile range [IQR])

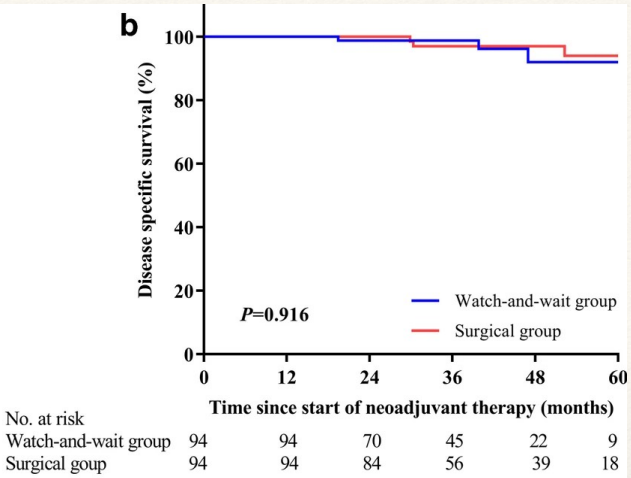
[a] *P* values were determined by $\chi 2$ test

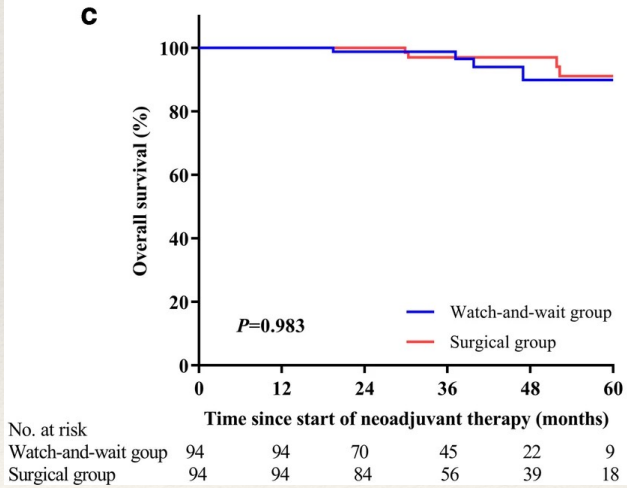
[b] *P* values were determined by Mann–Whitney U test

2010.1.30~2019.1.30　中国国内3施設共同

直腸診(DRE)、内視鏡、MRI/CTの3つで判定(Accuracy 98%)







【Regrowth】

術前化学療法+CRTで一旦縮小した腫瘍が再度局所で増大すること。Watch and Waitでは約25％でRegrowthがあるとされている

【結果】

1. 外科切除群の89.4％が術前化学療法+化学放射線療法を受けた
2. 外科切除(TME)では48名(51.1％)が病理学的完全奏効(pCR)
3. **肛門機能温存率 WW:92.6% vs Surgical:66%**
   特に肛門縁から3cm以内の場合は 89.7% vs 41.2%
4. 3年無遠隔転移率 WW:88% vs Surgical 89%
   WW群では局所の増大・再発なしで遠隔転移したのは4名/80名
5. WW群では14名がRegrowthするも、85.7％がR0切除を追加で受けた

CRT　RT 50Gy+ 5-FU or Capesitabine
※両群ともに術前に1剤以上の化学療法を受けていた

考察

- 局所増大Regrowthは、治療後2年以内に起きている
- サルベージ手術後(再発後追加手術後)の局所再発率は2群とも同程度
  →cCRが得られた場合には手術の遅延は問題にならない
- 既存の報告の遠隔転移率 8-8.9%と比較して、WW群は9.6%と同程度？
  考察ではcCRが得られても遠隔転移が認められた症例はあるが、
  手術群とWW群で遠隔転移が認められるまでの期間に差がなく、
  治療方針を決定した時点でミクロな遠隔転移があったのではないか？

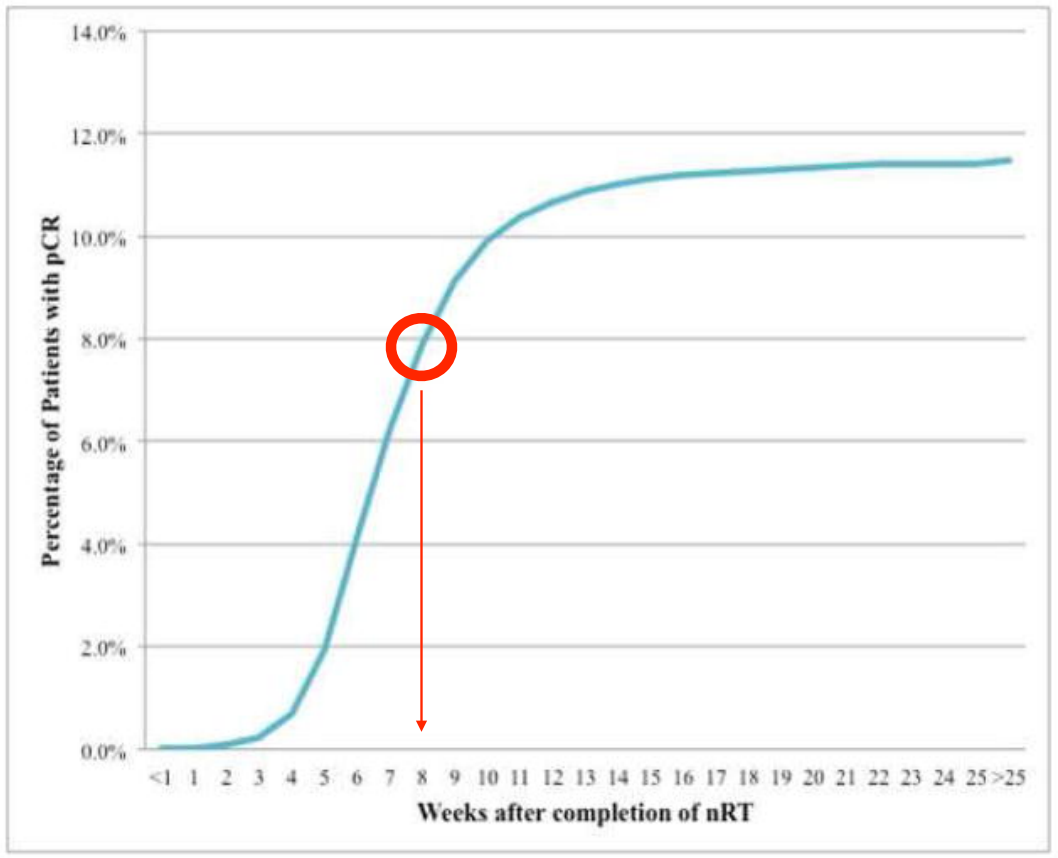
Limitations

1. Retrospective data Analysis
2. Quality Control of cCR assessment
3. No date of Quality of Life

NAT＆CRT後の外科切除まで期間：

57日(中央値)

pCRがもっと高くなった可能性？



Yuval JB, Garcia-Aguilar J. Watch-and-wait Management for Rectal Cancer After Clinical Complete Response to Neoadjuvant Therapy. Adv Surg. 2021;55:89-107.

フランスの多施設共同研究,Phase 3

局所進行直腸がんに対するFOLFIRINOX

P: 18-75歳 cT3-T4,M0(cStageII/III)のPS 0-1
　直腸がん患者

E(I): 術前化学療法としてFOLFIRINOX
　→化学放射線療法(Capecitabine+50Gy)

C: 化学放射線療法(Capecitabine+50Gy)

介入群、対照群とも外科切除+補助化学療法

O: Primary 3-years Disease Free survival
　Secondary OS, MFS, DSS…**QOL評価**

Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial

*Thierry Conroy, Jean-François Bosset, Pierre-Luc Etienne, Emmanuel Rio, Éric François, Nathalie Mesgouez-Nebout, Véronique Vendrely, Xavier Artignan, Olivier Bouché, Dany Gargot, Valérie Boige, Nathalie Bonichon-Lamichhane, Christophe Louvet, Clotilde Morand, Christelle de la Fouchardière, Najib Lamfichekh, Béata Juzyna, Claire Jouffroy-Zeller, Eric Rullier, Frédéric Marchal, Sophie Gourgou, Florence Castan, Christophe Borg, on behalf of the Unicancer Gastrointestinal Group and Partenariat de Recherche en Oncologie Digestive (PRODIGE) Group**

Lancet Oncol 2021; 22: 702–15

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See Comment page 575

*The full list of investigators is in the appendix

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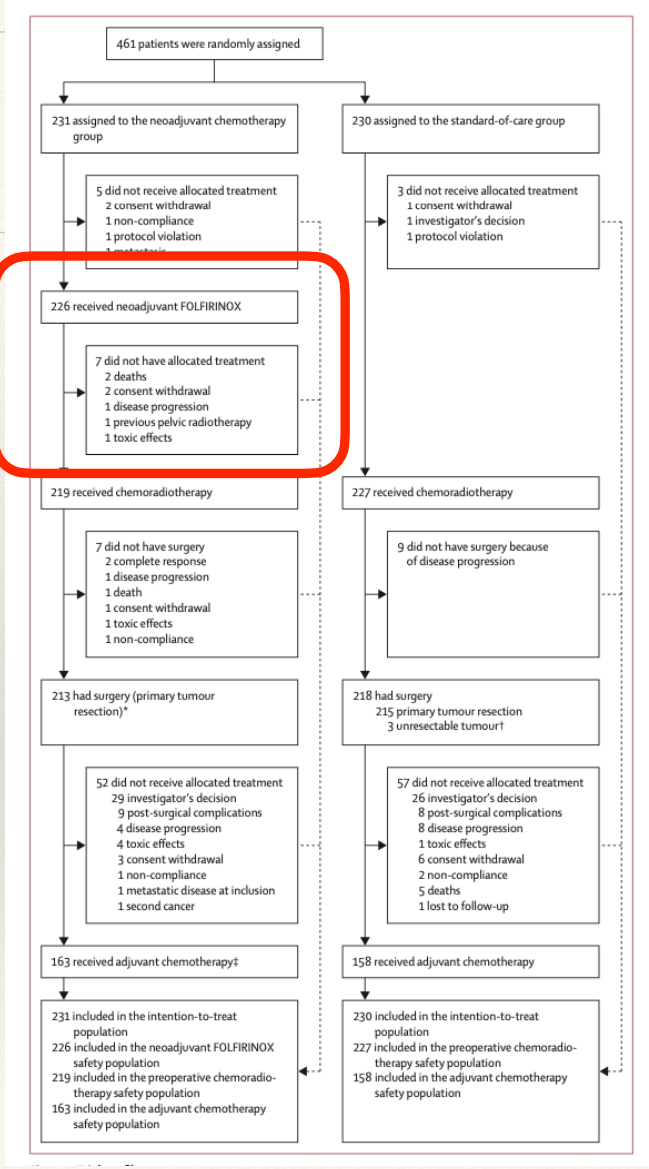
Summary

Background Treatment of locally advanced rectal cancer with chemoradiotherapy, surgery, and adjuvant chemotherapy controls local disease, but distant metastases remain common. We aimed to assess whether administering neoadjuvant chemotherapy before preoperative chemoradiotherapy could reduce the risk of distant recurrences.

Methods We did a phase 3, open-label, multicentre, randomised trial at 35 hospitals in France. Eligible patients were adults aged 18–75 years and had newly diagnosed, biopsy-proven, rectal adenocarcinoma staged cT3 or cT4 M0, with a WHO performance status of 0–1. Patients were randomly assigned (1:1) to either the neoadjuvant chemotherapy group or standard-of-care group, using an independent web-based system by minimisation method stratified by centre, extramural extension of the tumour into perirectal fat according to MRI, tumour location, and stage. Investigators and participants were not masked to treatment allocation. The neoadjuvant chemotherapy group received neoadjuvant chemotherapy with FOLFIRINOX (oxaliplatin 85 mg/m², irinotecan 180 mg/m², leucovorin 400 mg/m², and fluorouracil 2400 mg/m² intravenously every 14 days for 6 cycles), chemoradiotherapy (50 Gy during 5 weeks and 800 mg/m² concurrent oral capecitabine twice daily for 5 days per week), total mesorectal excision, and adjuvant chemotherapy (3 months of modified FOLFOX6 [intravenous oxaliplatin 85 mg/m² and leucovorin 400 mg/m², followed by intravenous 400 mg/m² fluorouracil bolus and then continuous infusion at a dose of 2400 mg/m² over 46 h every 14 days for six cycles] or capecitabine [1250 mg/m² orally twice daily on days 1–14 every 21 days]). The standard-of-care group received chemoradiotherapy, total mesorectal excision, and adjuvant chemotherapy (for 6 months). The primary endpoint was disease-free survival assessed in the intention-to-treat population at 3 years. Safety analyses were done on treated patients. This trial was registered with EudraCT (2011-004406-25) and ClinicalTrials.gov (NCT01804790) and is now complete.

Findings Between June 5, 2012, and June 26, 2017, 461 patients were randomly assigned to either the neoadjuvant chemotherapy group (n=231) or the standard-of-care group (n=230). At a median follow-up of 46·5 months (IQR 35·4–61·6), 3-year disease-free survival rates were 76% (95% CI 69–81) in the neoadjuvant chemotherapy group and 69% (62–74) in the standard-of-care group (stratified hazard ratio 0·69, 95% CI 0·49–0·97; p=0·034). During neoadjuvant chemotherapy, the most common grade 3–4 adverse events were neutropenia (38 [17%] of 225 patients) and diarrhoea (25 [11%] of 226). During chemoradiotherapy, the most common grade 3–4 adverse event was lymphopenia (59 [28%] of 212 in the neoadjuvant chemotherapy group *vs* 67 [30%] of 226 patients in the standard-of-care group). During adjuvant chemotherapy, the most common grade 3–4 adverse events were lymphopenia (18 [11%] of 161 in the neoadjuvant chemotherapy group *vs* 42 [27%] of 155 in the standard-of-care group), neutropenia (nine [6%] of 161 *vs* 28 [18%] of 155), and peripheral sensory neuropathy (19 [12%] of 162 *vs* 32 [21%] of 155). Serious adverse events occurred in 63 (27%) of 231 participants in the neoadjuvant chemotherapy group and 50 (22%) of 230 patients in the standard-of-care group (p=0·167), during the whole treatment period. During adjuvant therapy, serious adverse events occurred in 18 (11%) of 163 participants in the neoadjuvant chemotherapy group and 36 (23%) of 158 patients in the standard-of-care group (p=0·0049). Treatment-related deaths occurred in one (<1%) of 226 patients in the neoadjuvant chemotherapy group (sudden death) and two (1%) of 227 patients in the standard-of-care group (one sudden death and one myocardial infarction).

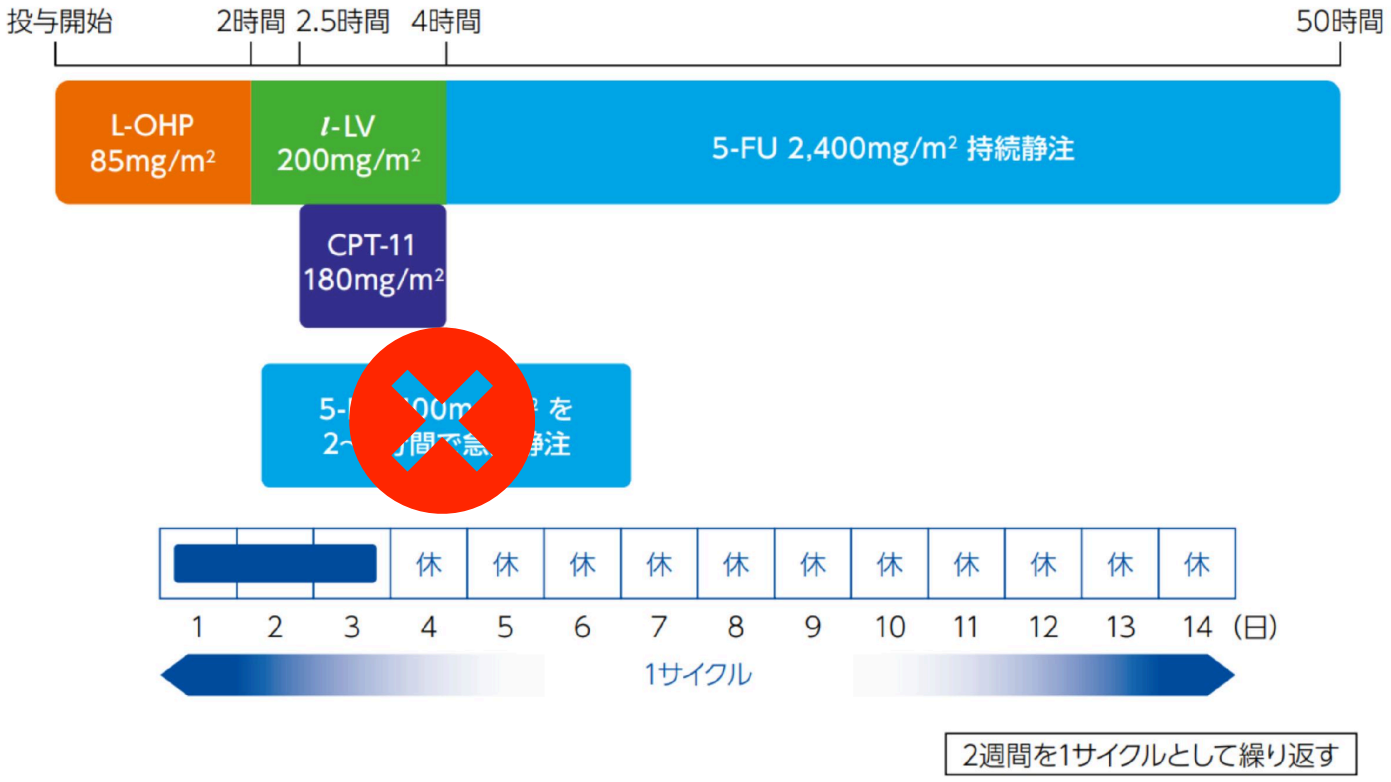
Interpretation Intensification of chemotherapy using FOLFIRINOX before preoperative chemoradiotherapy significantly improved outcomes compared with preoperative chemoradiotherapy in patients with cT3 or cT4 M0 rectal cancer. The significantly improved disease-free survival in the neoadjuvant chemotherapy group and the decreased neurotoxicity indicates that the perioperative approach is more efficient and better tolerated than adjuvant chemotherapy. Therefore, the PRODIGE 23 results might change clinical practice.



Patient& Method

1. 直腸がんは肛門縁から15cm以内
2. MRI,経肛門的超音波でT2は除外
3. 手術前に画像再評価して遠隔転移を除外
4. FOLFIRINOXは原法の用量(2週間毎) × 6サイクル
   ただし、 5 –FUの急速静注は省略
5. 放射線化学療法は週5日
   放射線照射日にCapecitabine内服
6. 放射線化学療法療法後、6-8週後に
   TME手術 ± 術後補助化学療法
   mFOLFOX × 12 (6週間)orCapecitabine × 8(24週)

2 投与スケジュール

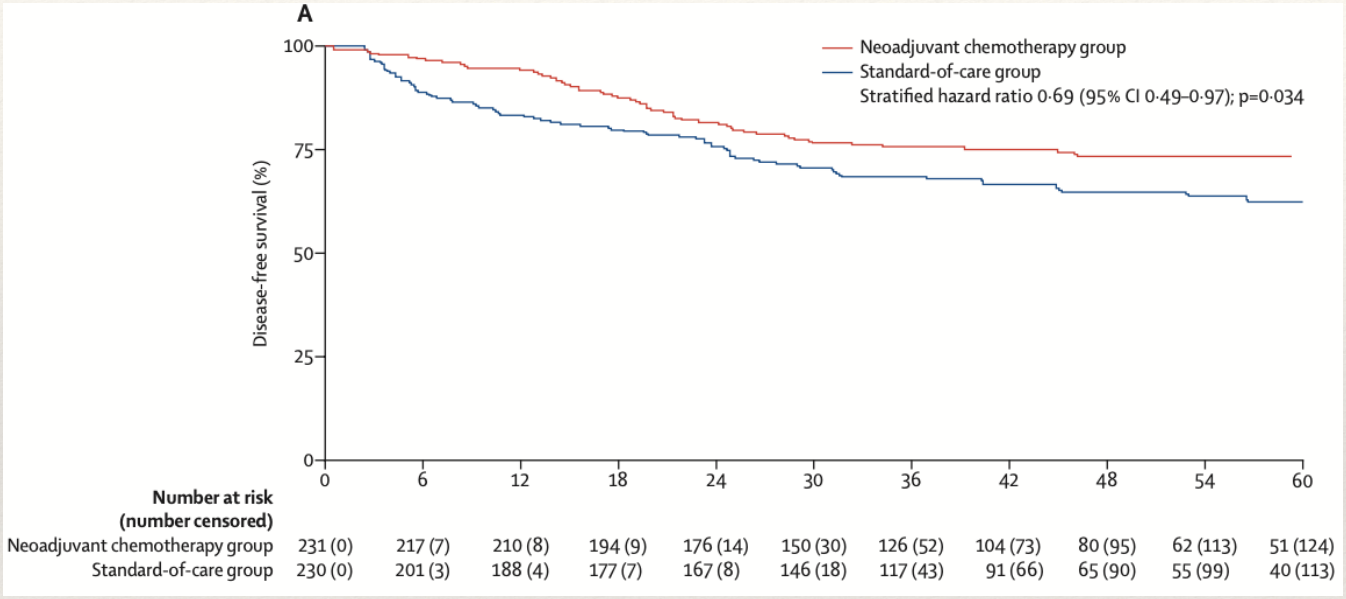


●本剤投与により、悪心、嘔吐、食欲不振などの消化器症状があらわれることがありますので、5-HT_3受容体拮抗剤、デキサメタゾン、選択的 NK_1受容体拮抗剤などによる前処置が推奨されます。

	Neoadjuvant chemotherapy group (n=231)	Standard-of-care group (n=230)
Age at randomisation, years		
Median (IQR)	61 (53–66)	62 (55–66)
Range	34–77	26–75
≥65	73 (32%)	85 (37%)
Sex		
Female	81 (35%)	74 (32%)
Male	150 (65%)	156 (68%)
WHO performance status		
0	178/229 (78%)	182/226 (81%)
1	51/229 (22%)	44/226 (19%)
Missing	2	4
Distance to anal verge,* cm		
≤5	87 (38%)	83 (36%)
5·1–10	114 (49%)	118 (51%)
10·1–15	30 (13%)	29 (13%)
MRI T stage*		
T2	3/225 (1%)	2/225 (1%)
T3	182/225 (81%)	188/225 (84%)
T3a	17/225 (8%)	17/225 (8%)
T3b	77/225 (34%)	92/225 (41%)
T3c	73/225 (32%)	64/225 (28%)
T3d	15/225 (7%)	15/225 (7%)
T4	40/225 (18%)	35/225 (16%)
T4a	3/225 (1%)	4/225 (2%)
T4b	37/225 (16%)	31/225 (14%)
Missing	6	5
cN at inclusion*		
0†	24 (10%)	22 (10%)
1	148 (64%)	155 (67%)
2	59 (26%)	53 (23%)
Enlarged lateral nodes	23 (10%)	24 (10%)
Predicted radial mesorectal margin,* mm		
≤1	48 (21%)	54 (23%)
>1	137 (59%)	141 (61%)
Missing	46 (20%)	35 (15%)
Presence of distant metastasis*	5 (2%)	5 (2%)

- 両群でBase lineに大きな差はない　側方リンパ節腫大 が約10％

Results



手術を受けなかった術前FOFIRINOX 群の患者

・T3N2でも59.5ヶ月臨床的完全奏効を維持

・T4bN0でも62.1ヶ月臨床的完全奏効を維持

1. FOFIRINOX の完遂率 92%

   80% 以上が予定の投与量を維持

2. Grade3-4 好中球減少 17 %

   Grade3-4 下痢 11%

   発熱性好中球減少　2%

3. TME切除 92% vs 95%

   人工肛門回避率は14% vs 15%

   R0切除率　95% vs 94 %

4. **Clavien-Dindo IV-V complication**

   術前化学療法群が有意に少なかった！

Results

Pathological complete response rate (ypT0N0)			<0·0001
Yes	59/212 (28%)	26/215 (12%)	..
No	153/212 (72%)	189/215 (88%)	..
Missing	1	3	..
Neoadjuvant rectal score			<0·0001
Median (IQR)	8·4 (0·9–15·0)	15·0 (8·4–20·4)	..
Mean (SD)	11·2 (10·7)	16·1 (13·4)	..
Missing	2	4	..

【QOL評価】

QLQ -C30質問票使用

FOFIRINOX群: 85％回収率

Standard- care: 84％回収率

→後日別論文で報告

【補助化学療法施行率】

Neo-adjuvant: 77%
Standard-care: 79%

- KRAS,NRAS,BRAF,MSI-Hなど遺伝子異常は配慮されていない

本日のまとめ

- 局所進行直腸がんは外科切除が第一選択ではない時代がくるかもしれない
- 直腸がんの術前放射線化学療法は手術の合併症も少なくするかもしれない

本日の文献一覧

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