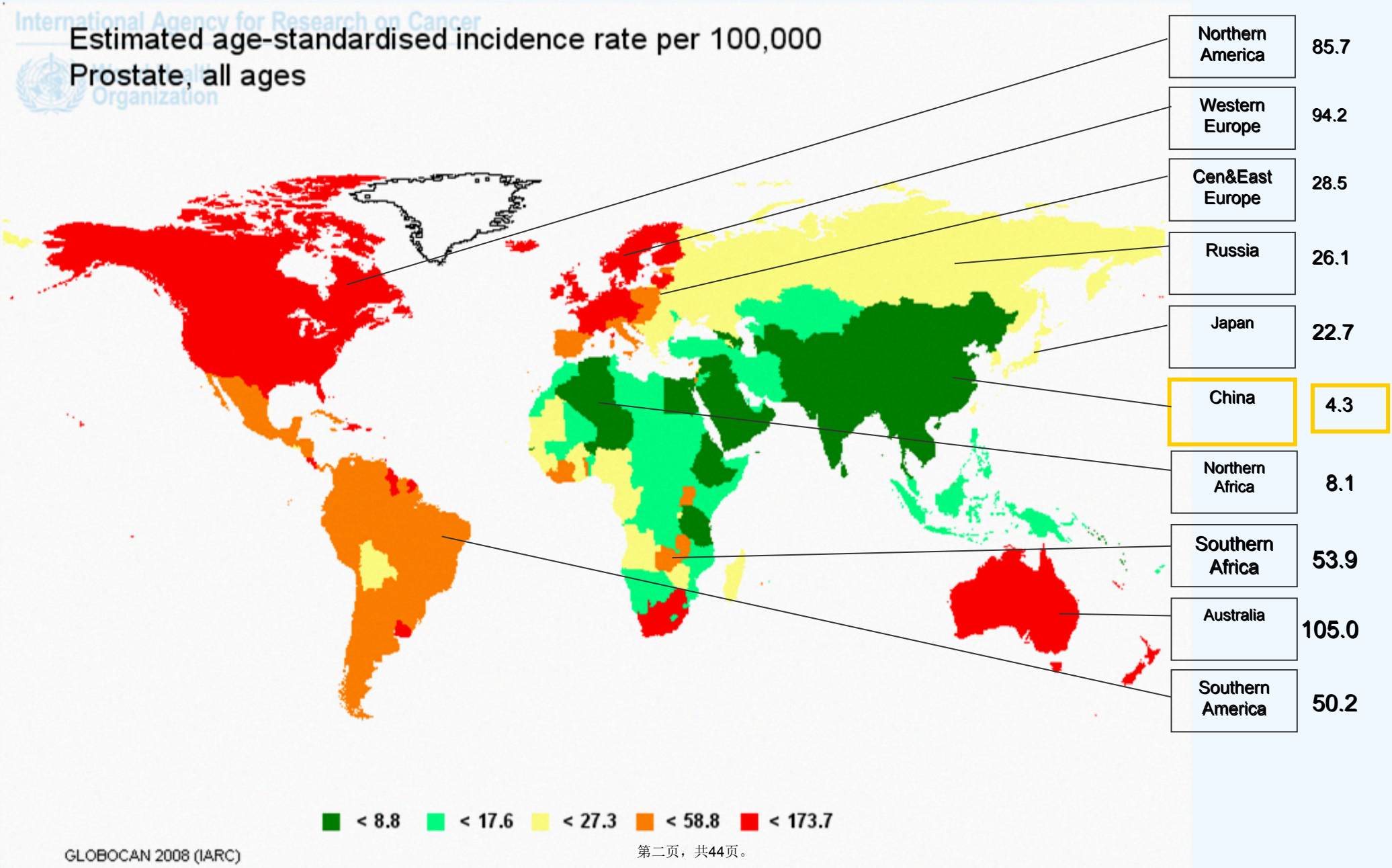
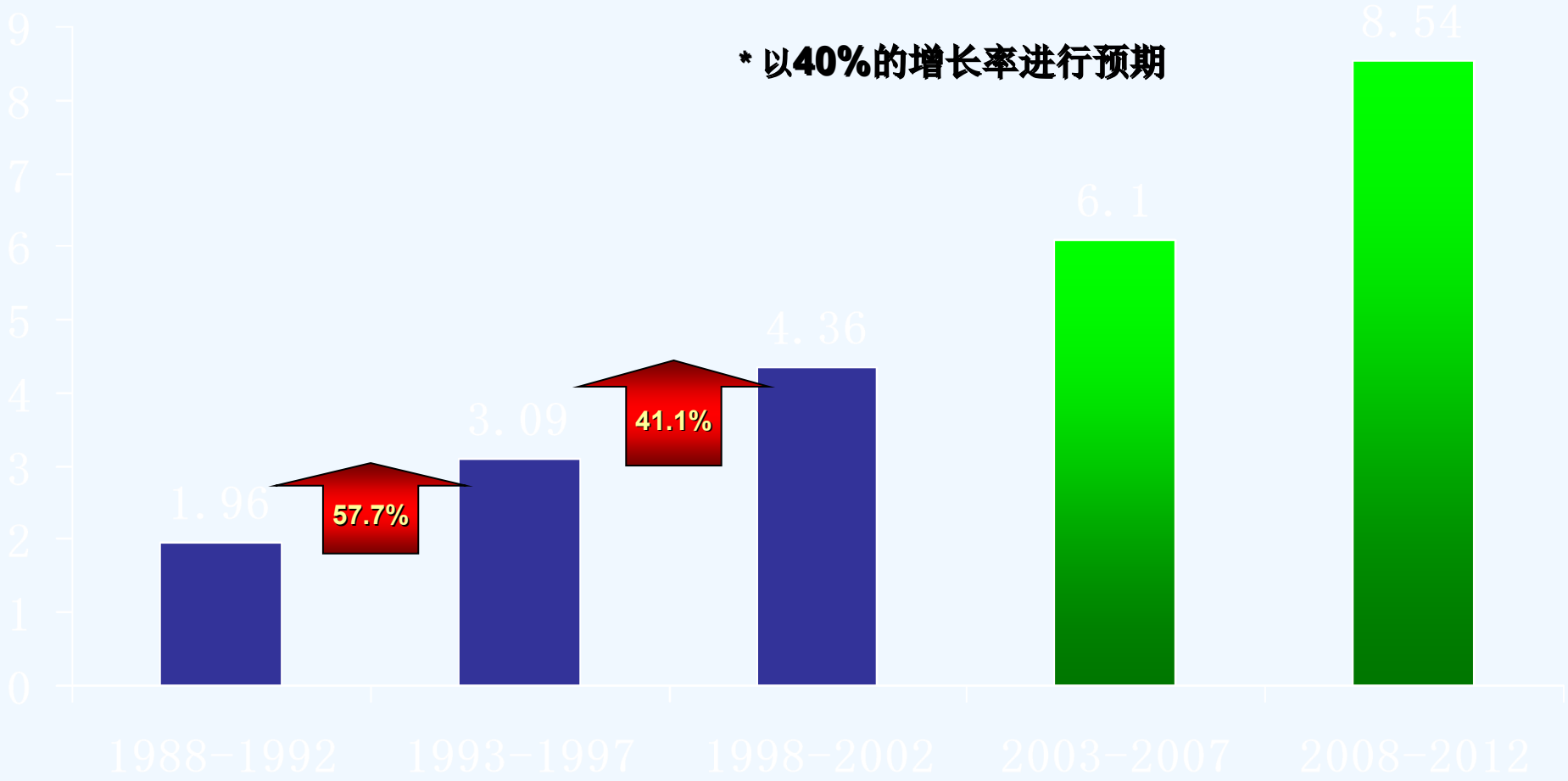
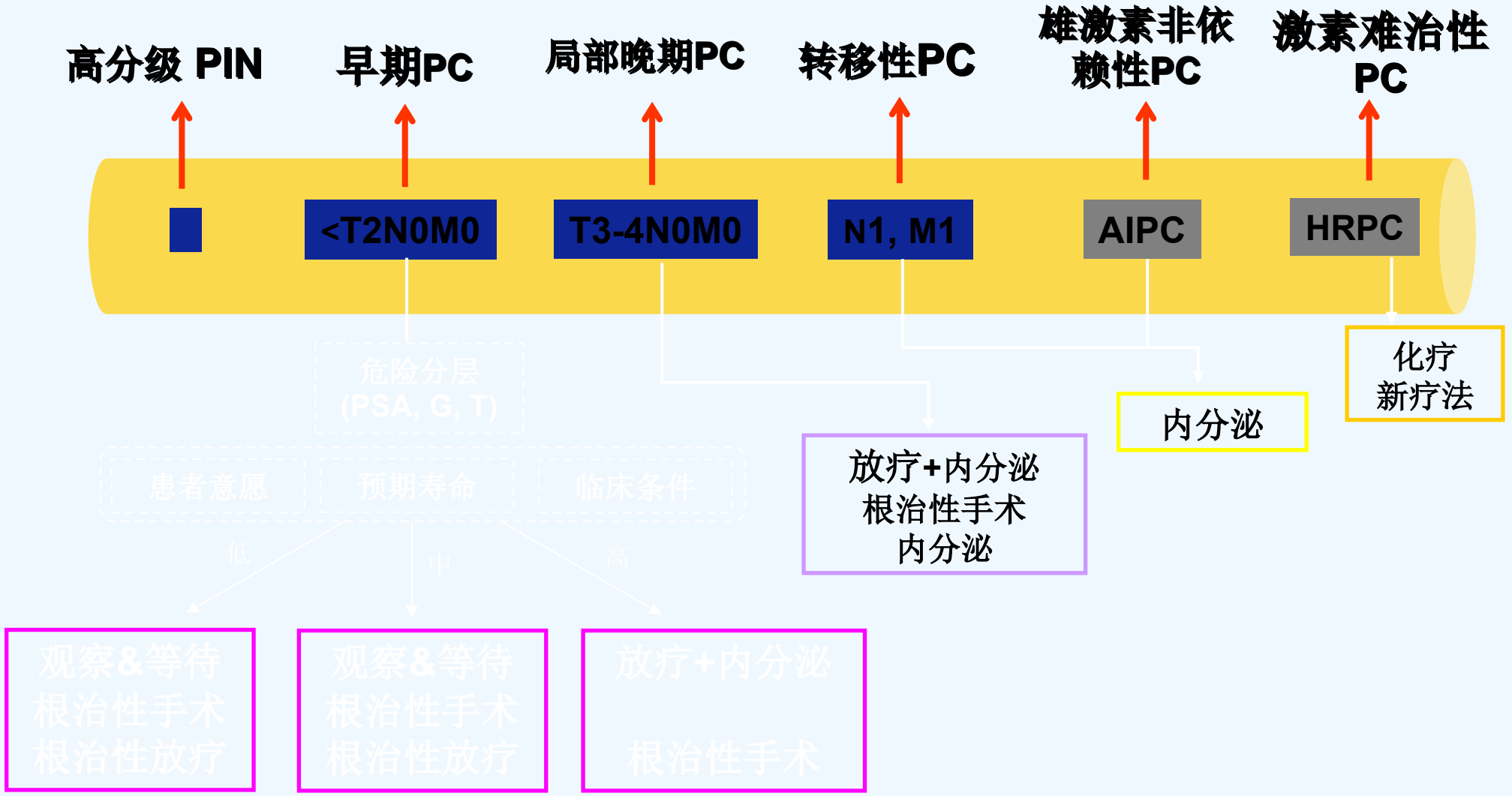
前列腺癌化疗


International Agency for Research on Cancer
World Health Organization
Estimated age-standardised incidence rate per 100,000
Prostate, all ages
Northern America
85.7
Western Europe
94.2
Cen&East Europe
28.5
Russia
26.1
Japan
22.7
China
4.3
Northern Africa
8.1
Southern Africa
53.9
Australia
105.0
Southern America
50.2
< 8.8
< 17.6
< 27.3
< 58.8
< 173.7
GLOBOCAN 2008 (IARC)

（/10万人）


* 以40%的增长率进行预期
9
8
7
6
5
4
3
2
1
0
1.96
3.09
4.36
6.1
8.54
57.7%
41.1%
1988-1992
1993-1997
1998-2002
2003-2007
2008-2012


高分级 PIN
早期PC
局部晚期PC
转移性PC
雄激素非依赖性PC
激素难治性PC
<T2N0M0
T3-4N0M0
N1, M1
AIPC
HRPC
化疗
新疗法
内分泌
放疗+内分泌
根治性手术
内分泌
危险分层
(PSA, G, T)
患者意愿
预期寿命
临床条件
低
中
高
观察&等待
根治性手术
根治性放疗
观察&等待
根治性手术
根治性放疗
放疗+内分泌
根治性手术

中、美前列腺癌现状差异

- 对京、沪、穗三个中心525例前列腺癌患者的分析显示[1]：
  - 68.0%的患者确诊时已属于晚期前列腺癌，80.2%的患者以内分泌治疗为主要治疗手段
  - 晚期前列腺癌患者从一线内分泌治疗发展到激素抵抗性前列腺癌（HRPC）的中位时间为20个月（6～73个月）

- 美国和欧洲[2]
  - 无症状前列腺癌占60.0%
  - 95.0%的患者在确诊时肿瘤局限

1. 马春光 等，中华外科杂志 2008, 46(12): 921-5
2. Murphy AM et al. J Urol 2004, 25: 95-9

- 雄激素非依赖性前列腺癌（AIPC）
  - –阶段：激素非依赖发生的早期，有些患者对二线内分泌治疗仍有效
  - –定义：间隔2周连续2～3次血清PSA升高；血清睾酮保持去势水平
  - –治疗：二线内分泌治疗，化疗等
- 激素难治性前列腺癌（HRPC）
  - –阶段：二线内分泌治疗无效或二线内分泌治疗后病变仍继续发展
  - –定义：应至少同时具备以下①～④

    ①血清睾酮达去势水平（＜50 ng/dl）；

    ②间隔2周连续3次血清PSA升高；

    ③抗雄激素撤退治疗4周以上；

    ④二线内分泌治疗期间PSA进展；

    ⑤骨或软组织转移病变有进展。
  - –治疗：化疗等
- 去势抵抗前列腺癌（CRPC）：一种更准确的提法
  - –定义：睾酮维持在去势水平，但疾病出现进展（PSA升高，病灶增大，新病灶……）

- 单纯PSA升高 52周
- PSA升高，有小转移灶，无症状 41-52周
- PSA升高，较大转移灶，无症状 10-28周
- PSA升高，有小转移灶，有症状 32-41周
- PSA升高，较大转移灶，有症状 10-28周

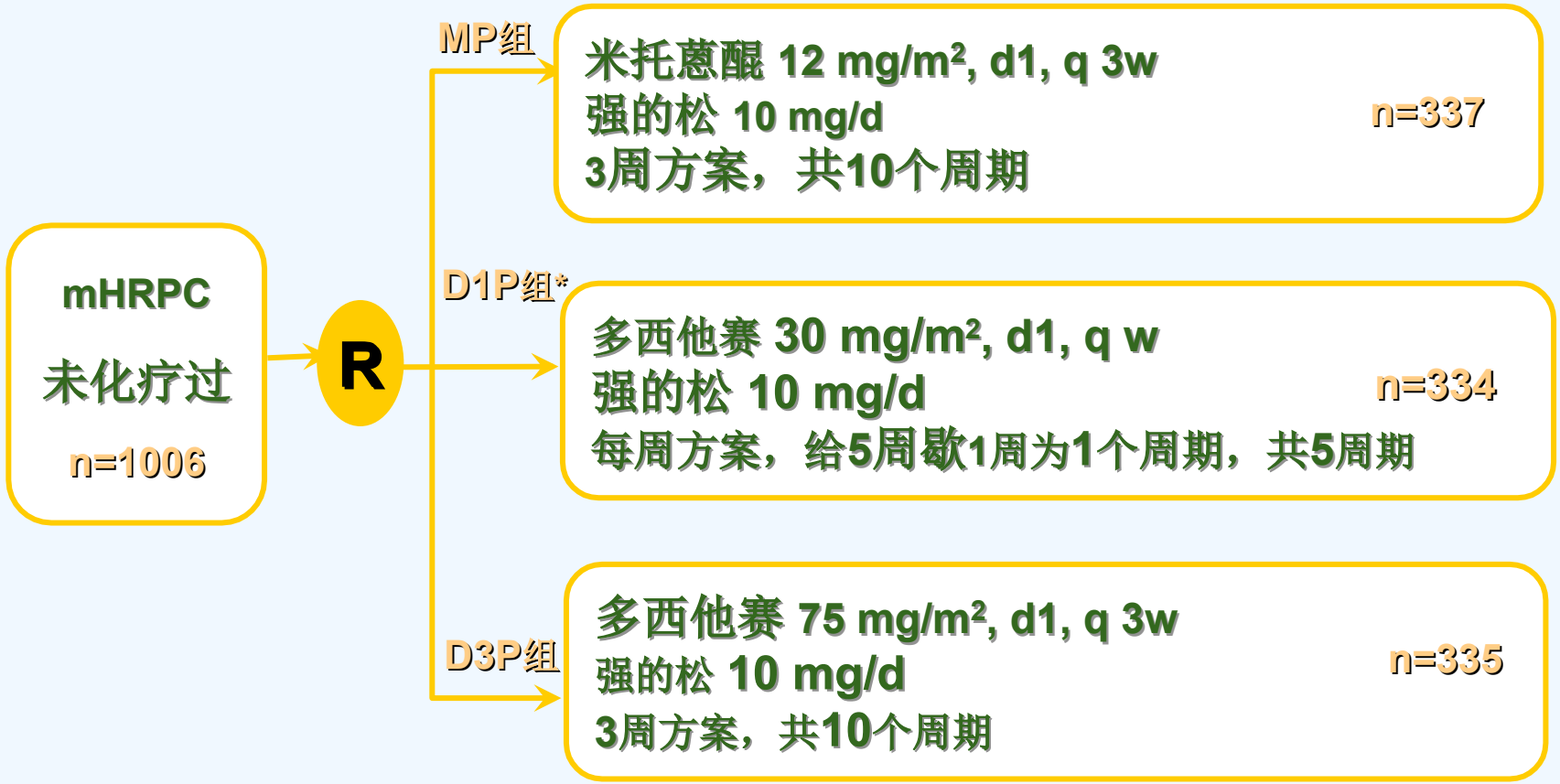
Eur Urol 2001; 39:121-130

PRINCIPLES OF CHEMOTHERAPY/IMMUNOTHERAPY

- Men with advanced prostate cancer should be encouraged to participate in clinical trials and referred early to a medical oncologist.
- Systemic chemotherapy should be reserved for men with castration-recurrent metastatic prostate cancer except when studied in clinical trials.
- Every 3-week docetaxel and prednisone is the preferred first-line chemotherapy treatment based upon phase 3 clinical trial data for men with symptomatic castration-recurrent prostate cancer. Symptomatic patients who are not candidates for docetaxel-based regimens could be treated with mitoxantrone and prednisone.
- Men with castration-recurrent metastatic prostate cancer who are symptomatic should be considered for chemotherapy.
- Men with less advanced disease may consider a new immunotherapy.
  - Sipuleucel-T has been shown in a Phase 3 clinical trial to extend mean survival from 21.7 mo in the control arm to 25.8 mo in the treatment arm, which constitutes a 22% reduction in mortality risk.
  - Sipuleucel-T is well tolerated; common complications include chills, pyrexia, and headache.
  - Sipuleucel-T may be considered for men with castration-recurrent metastatic prostate cancer who have:
    - good performance status (ECOG 0-1)
    - estimated life expectancy > 6 mo
    - no visceral disease
    - no or minimal symptoms

- Only regimens utilizing docetaxel on an every 3 week schedule demonstrated beneficial impact on survival. The duration of therapy should be based on the assessment of benefit and toxicities. In the pivotal trials establishing survival advantage of docetaxel-based chemotherapy, patients received up to 10 cycles of treatment if no progression and no prohibitive toxicities were noted.
- Rising PSA should not be used as the sole criteria for progression. Assesment of response should incorporate clinical and radiographic criteria.
- Men who have failed docetaxel-based chemotherapy should be encouraged to participate in clinical trials. However, cabazitaxel with prednisone has been shown in a randomized phase 3 study to prolong overall survival, progression-free survival, and PSA and radiologic responses when compared with mitoxantrone and prednisone and is FDA approved in the post-docetaxel second line setting. Selection of patients without severe neuropathy and adequate liver, kidney, and bone marrow function is necessary, given the high risk of neutropenia and other side effects in this population, with consideration of prophylactic granulocyte growth factor injections.
- Mitoxantrone has not demonstrated a survival improvement in this post-docetaxel setting but remains a palliative therapeutic option, particularly in men who are not candidates for cabazitaxel therapy. No chemotherapy regimen to date has demonstrated improved survival or quality of life following cabazitaxel, and trial participation should be strongly encouraged. Outside of a clinical trial, several systemic agents have shown palliative benefits in single arm studies. Treatment decisions should be individualized based on comorbidities and functional status. Finally, for patients who have not demonstrated definitive evidence of progression on prior docetaxel therapy, retreatment with this agent can be attempted.

指南	机构	推荐
NCCN 2011.1	美国国家综合癌症网络	*mCRPC的化疗原则：* 一线化疗首选**多西他赛联合强的松**3周方案，其他可选方案包括多西他赛联合雌二醇氮芥3周方案和米托蒽醌联合强的松3周方案，但仅多西他赛3周方案被证实有生存益处 **cabazitaxel联合强的松**为多西他赛失败后的二线化疗 （推荐级别：均为1类#）
EAU 2010	欧洲泌尿外科学会	*mCRPC的化疗：* 多西他赛 75mg/m^2 q3w 有生存益处，cabazitaxel是多西他赛失败后的有效二线治疗 （推荐级别：A级*）
CUA 2009	中国泌尿外科学会	*HRPC的化疗：* Docetaxel 75mg/m^2 q3w+强的松10 mg/d，共10个周期



主要终点：

OS

次要终点：

疼痛缓解

QoL改善

PSA缓解

肿瘤缓解

分层因素：

①基线疼痛水平：中位PPI评分 ≥ 2或平均镇痛评分（AS）≥10 vs. PPI < 2或AS < 10

②KPS评分: ≤70 vs. ≥ 80

Tannock IF, et al. N Engl J Med 2004; 351:1502–12

* 每周方案未获批准

（1）

	D3P组 (n=335)	D1P组 (n=334)	MP组 (n=337)
中位年龄（岁）	**68**	**69**	**68**
Gleason评分			
≤7	42%	40%	42%
8—10	31%	31%	28%
未明	26%	29%	30%
既往治疗			
前列腺根治术	**19%**	**24%**	**21%**
放疗	**52%**	**44%**	**51%**
雌二醇氮芥	**19%**	**18%**	**20%**
既往内分泌治疗			
1种	9%	8%	6%
2种	68%	72%	69%
>2种	23%	21%	25%
KPS评分≤70	**13%**	**12%**	**14%**

Tannock IF, et al. N Engl J Med 2004; 351:1502–12

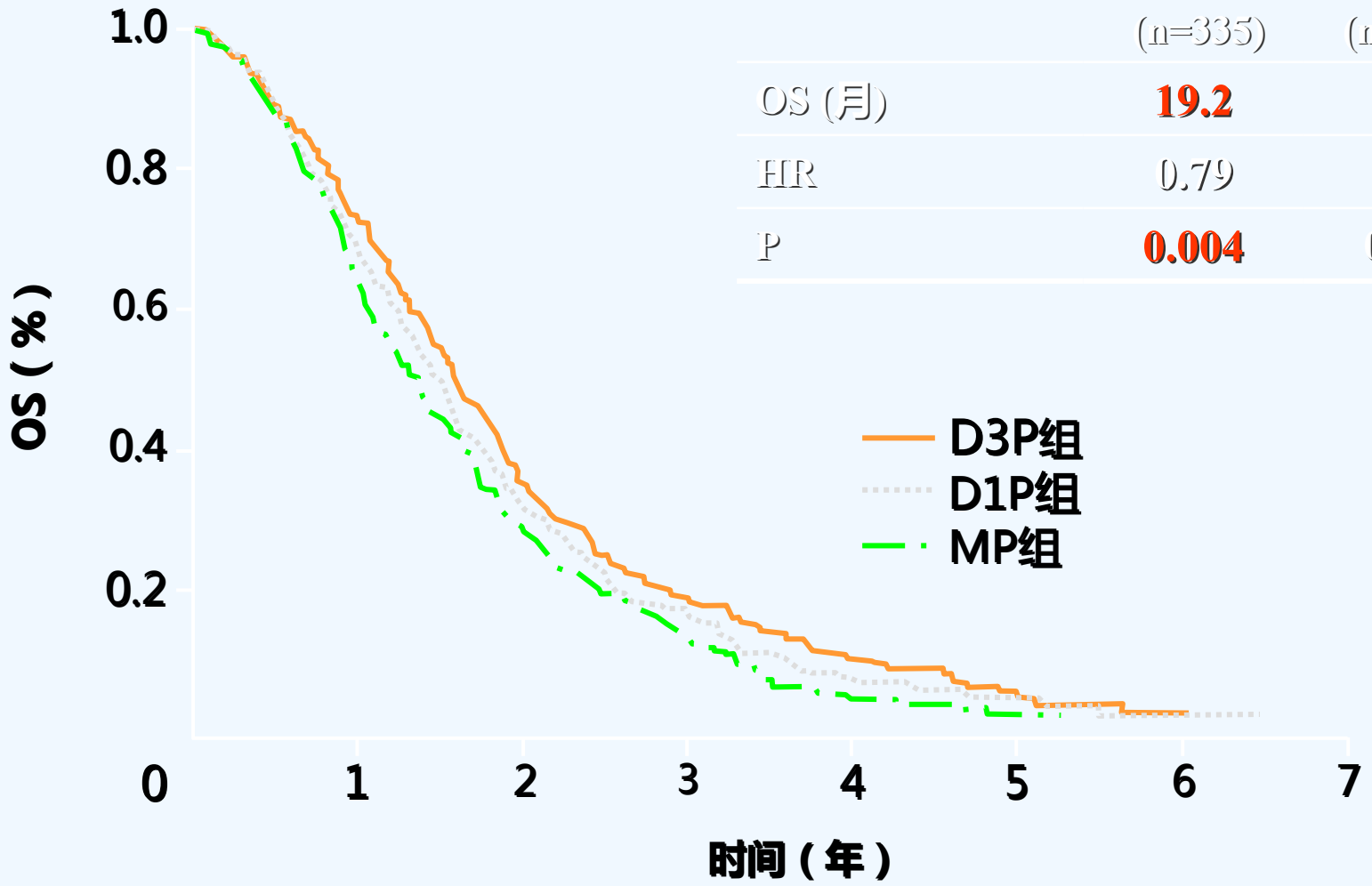
	D3P组 (n=335)	D1P组 (n=334)	MP组 (n=337)
疼痛*	45%	45%	46%
血清PSA			
中位值（ng/ml）	114	108	123
≥20 ng/ml	87%	84%	89%
疾病范围			
骨转移	90%	91%	92%
内脏疾病	22%	24%	22%
可测量病变	40%	39%	40%
入组时进展证据#			
骨扫描	71%	69%	69%
可测量病变增大	28%	30%	28%
不可测量病变增大	13%	16%	15%
PSA升高	72%	66%	68%

*疼痛定义为PPI评分≥2或AS≥10 #患者可能存在一个以上的疾病进展指征

Tannock IF, et al. N Engl J Med 2004; 351:1502–12

（2008年）

	D3P组 (n=335)	D1P组 (n=334)	MP组 (n=337)
OS (月)	**19.2**	17.8	**16.3**
HR	0.79	0.87	1.00
P	**0.004**	0.086	



Berthold DR, et al. JCO 2008; 26:242–5

	D3P组	D1P组	MP组
疼痛*			
评估人数	153	154	157
缓解情况			
缓解率	**35%**	31%	**22%**
95% CI	27%—43%	24%—39%	16%—29%
P值	**0.01**	0.08	
血清PSA下降≥50%			
评估人数	291	282	300
缓解情况			
缓解率	**45%**	48%	**32%**
95% CI	40%—51%	42%—54%	26%—37%
P值	**< 0.001**	< 0.001	

*疼痛缓解定义为PPI评分下降2分且AS无升高，或者AS下降≥50%且PPI无评分升高，且都持续≥3周

Tannock IF, et al. N Engl J Med 2004; 351:1502–12

	D3P组	D1P组	MP组
肿瘤缓解			
评估人数	141	134	137
缓解情况			
缓解率	**12%**	8%	**7%**
95% CI	7%—19%	4%—14%	3%—12%
P值	**0.11**	0.59	
QoL			
评估人数	278	270	267
缓解情况*			
缓解率	**22%**	23%	**13%**
95% CI	17%—27%	18%—28%	9%—18%
P值	**0.009**	0.005	

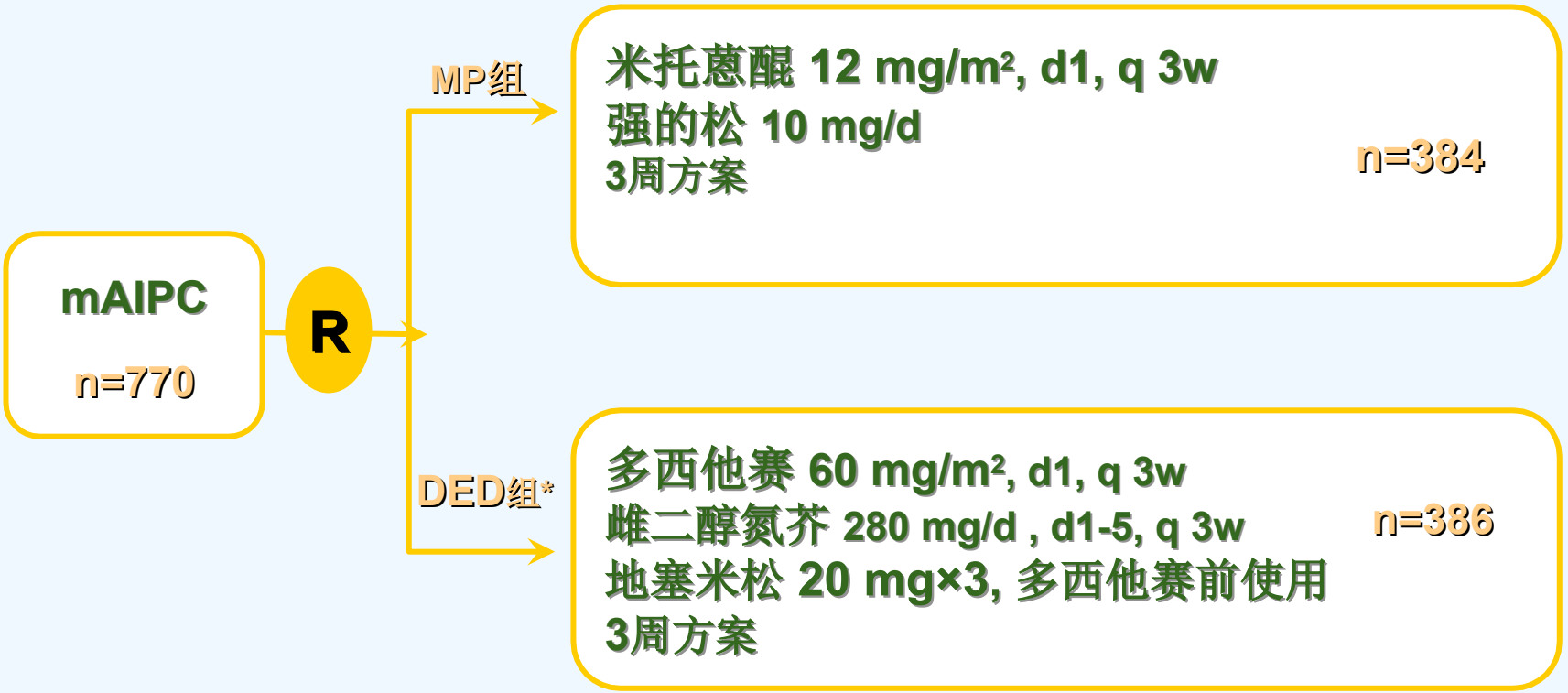
*QoL改善定义为至少相隔3周的2次评估显示FACT-P评分比基线时改善16点

Tannock IF, et al. N Engl J Med 2004; 351:1502–12

- 及米托蒽醌联合强的松3周方案相比，多西他赛联合强的松3周方案所致总生存期更长，并有助于提高疼痛缓解率和，提高血清PSA缓解率，以及改善患者的生活质量
  - –OS延长（19.2 vs. 16.5个月，HR=0.79，P=0.004）
  - –提高PSA缓解率（45% vs. 32%，P<0.001）
  - –提高疼痛缓解率（35% vs. 22%，P=0.01）
  - –改善生活质量（22% vs. 13%，P=0.009）
- 多西他赛3周方案的安全性和可耐受性及既往的报告一致

Tannock IF, et al. N Engl J Med 2004; 351:1502–12

Berthold DR, et al. JCO 2008;26:242–5



分层因素：

①进展类型：可测量或评估的转移性疾病 vs. 仅有PSA升高

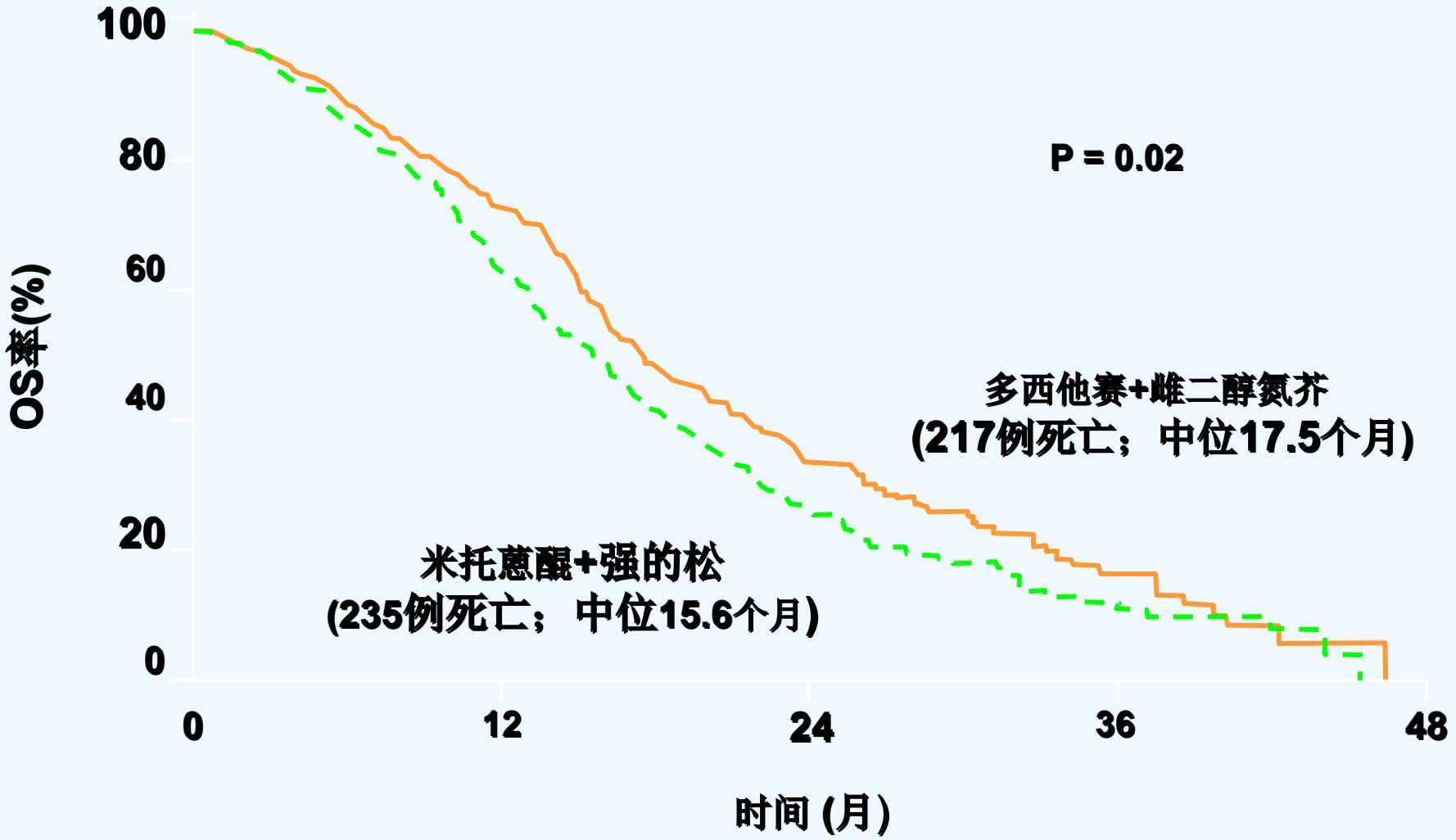
②疼痛分级：1级 vs. 2级 vs. 3级 vs. 4级

③SWOG PS评分：0-1 vs. 2 vs. 3

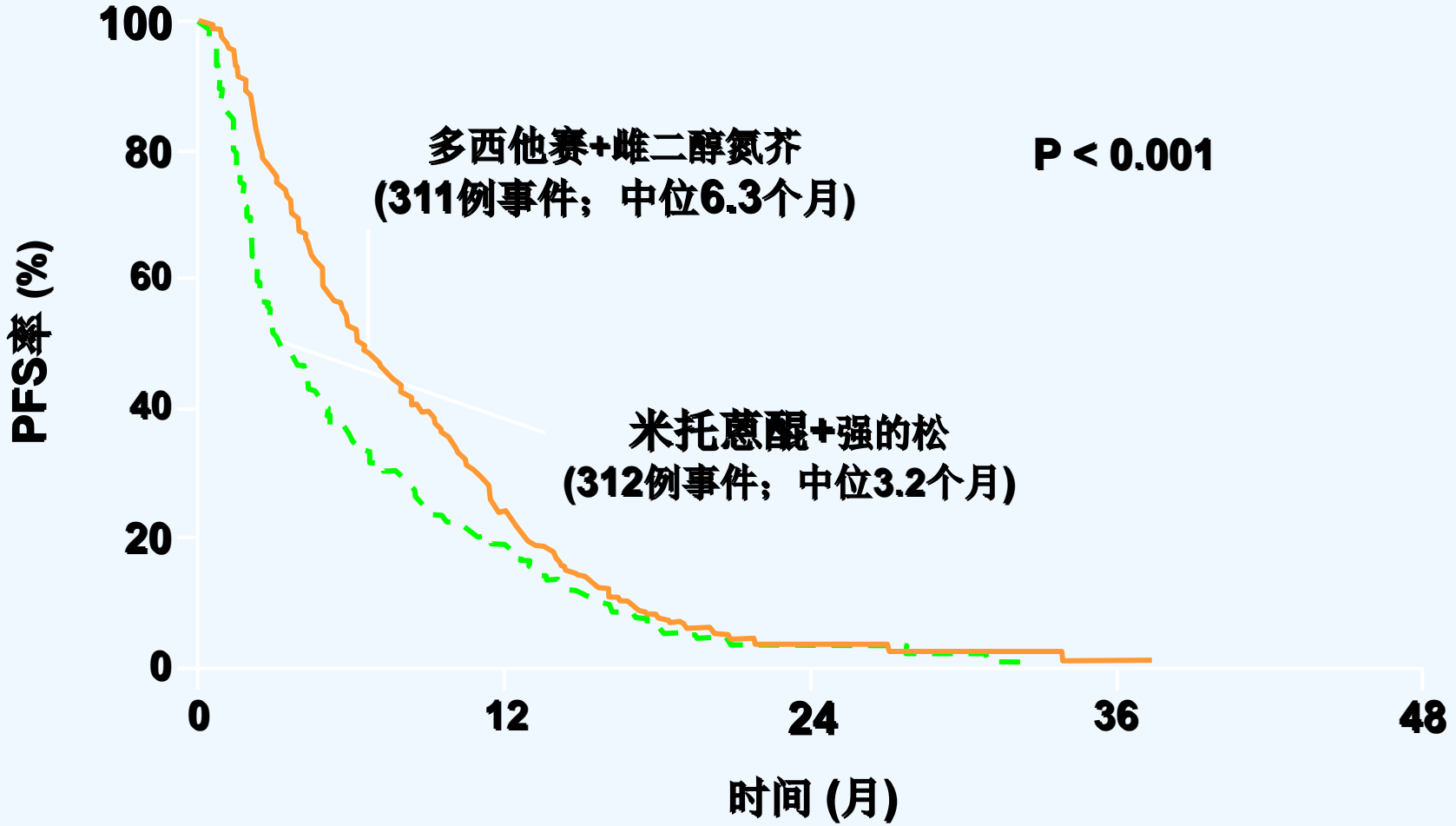
Petrylak DP, et al. NEJM 2004; 351:1513-1520.

	DED组 （n=386）	MP组 （n=384）
年龄 (岁)	**70（47-88）**	**70（43-87）**
种族或族裔 (%)		
白人/黑人/西班牙/亚洲/未知	86/12/7/1/1	82/15/6/1/1
SWOG PS评分 (%)		
0或1/ 2 或3	**90/10**	**88/12**
进展类型 (%)		
可测量或可评估/仅PSA升高	81/19	82/18
PSA (ng/ml)		
中位/范围	**84/ 0.1-10820**	**90/ 0.1-8378**
疾病位置 (%)		
骨/软组织 (淋巴结/肝/肺)	84 (24/8/10)	88 (26/9/10)
骨痛 (%)		
<2级/≧2级	**64/36**	**64/36**

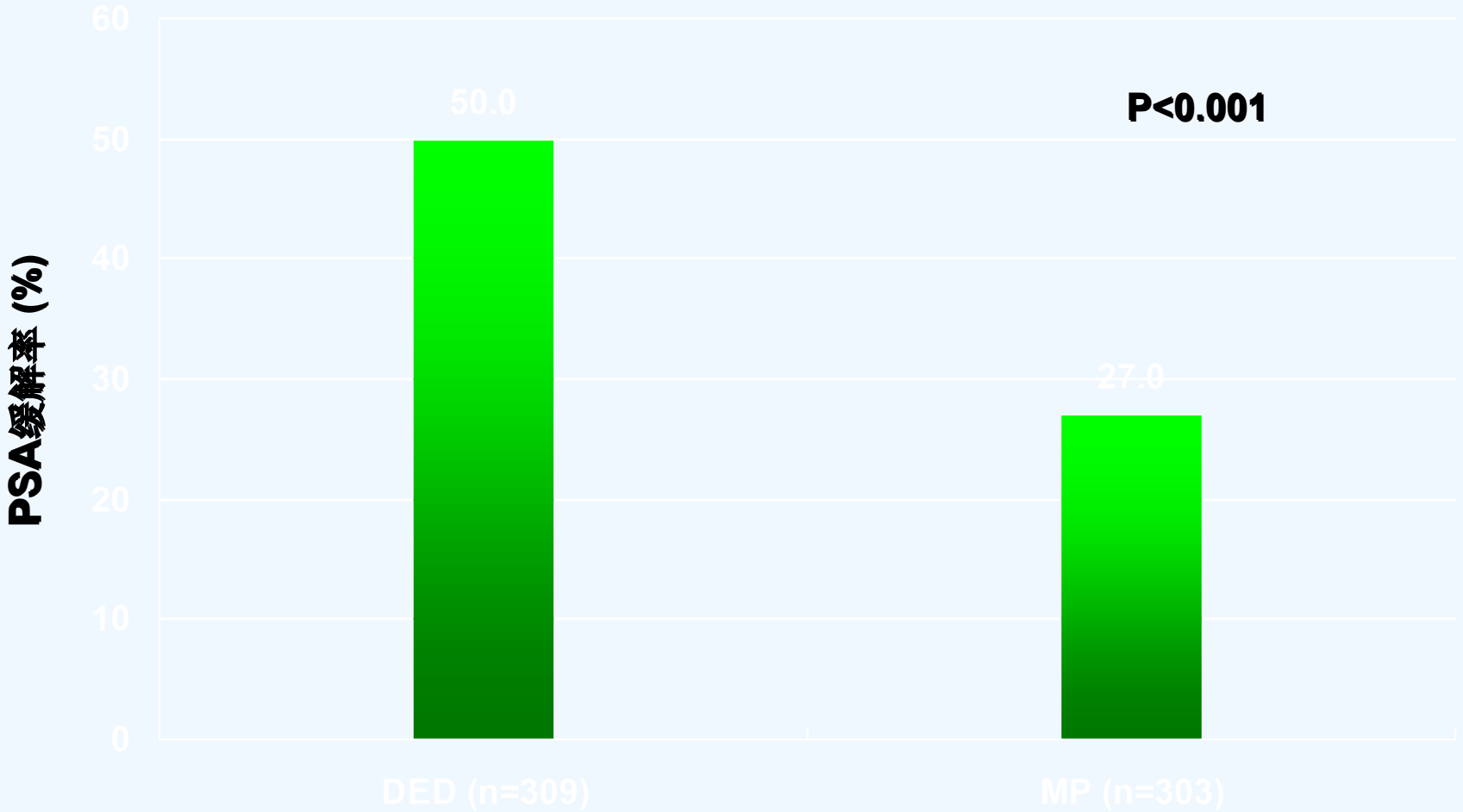
Petrylak DP, et al. NEJM 2004; 351:1513-1520.



Petrylak DP, et al. NEJM 2004; 351:1513-1520.



Petrylak DP, et al. NEJM 2004; 351:1513-1520.



* 血清PSA降低≥50%的患者比例

Petrylak DP, et al. NEJM 2004; 351:1513-1520.

- 及米托蒽醌联合强的松方案相比，多西他赛联合雌二醇氮芥使中位总生存期延长了近2个月，这就支持该方案在mAIPC患者中的使用
  - OS延长（17.5 vs. 15.6个月，HR=0.80，P=0.02）
  - 提高PSA缓解率（50% vs. 27%，P<0.001）
- 多西他赛的安全性和可耐受性及既往的报告一致

Petrylak DP, et al. NEJM 2004; 351:1513-1520.