NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview of salvage cryotherapy for recurrent prostate cancer

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) advise on the safety and efficacy of an interventional procedure previously reviewed by SERNIP. It is based on a rapid survey of published literature, review of the procedure by Specialist Advisors and review of the content of the SERNIP file. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was updated by NICE in June 2004.

Procedure names

- Salvage cryotherapy for recurrent prostate cancer.
- Secondary transperineal cryotherapy for carcinoma of the prostate.
- Salvage cryosurgery for recurrent prostate cancer.
- Salvage cryoablation for recurrent prostate cancer.

Specialty society

- British Association of Urological Surgeons.

Description

Indications

Prostate cancer is one of the most common cancers in men. It tends to affect older men, with the risk rising with age. It is not a single disease entity but rather a spectrum of disease ranging from very aggressive to slow growing tumours, which may or may not cause any symptoms or shorten life.

Symptoms, when they occur, include urinary outflow obstruction and features of metastasis, such as bone pain.

Current treatments and alternatives

Treatment options for patients with locally recurrent prostate cancer after radiotherapy treatment are somewhat limited and include salvage radical prostatectomy, salvage cryotherapy, salvage brachytherapy, and high intensity focused ultrasound therapy. Salvage cryotherapy is less invasive than salvage

radical prostatectomy and recent advances in the technique have helped to decrease the morbidity of the procedure by sparing the surrounding structures such as the rectum.

What the procedure involves

Salvage cryotherapy may be performed under general or spinal anaesthesia. A warming catheter is initially inserted into the urethra, to prevent it being damaged by the cold. Cryoneedles or probes are inserted into the prostate, using imaging for guidance. Temperature monitor probes may also be placed percutaneously through the perineum. Argon gas is then circulated through these needles or probes generating very low temperatures and causing the formation of ice around the prostate gland, which destroys the tissue. Newer cryotherapy techniques allow for these needles to be removed or repositioned so that the frozen zone conforms to the exact size and shape of the target tissue.

After the procedure, a catheter is inserted and left in place for 1–2 weeks, depending on the post-void residual urine volume.

Efficacy

The evidence of efficacy is based on a number of case series studies. The results of these studies indicate that some patients have negative biopsies, lower prostate specific antigen (PSA) levels and experience biochemical-disease-free survival following cryotherapy. Biochemical-disease-free survival varied among the studies depending on how it was measured. In one study of 59 patients with a median follow-up of 82 months, biochemical-disease-free survival using a PSA cut off of 0.5 nanograms/ml was 59%. While in another study of 39 patients using a PSA cut off of 0.3 nanograms/ml 74% of patients were free of biochemical recurrence at 24 months.

The different efficacy outcome measures used in the studies makes comparisons of efficacy across studies difficult. Few studies reported on long-term outcomes and the conclusions are largely based on biochemical-disease-free survival as a surrogate outcome measure for clinical disease recurrence.

The Specialist Advisors considered there to be insufficient evidence to demonstrate efficacy for the procedure.

Safety

Complication rates varied among the studies and there is some evidence to suggest that complications have decreased with improvements in technique and instrumentation. In one study of 118 patients, four (3%) developed a rectal fistula following the procedure, with eight (7%) patients experiencing severe incontinence. Other complications in this study included outlet obstruction (10/118), urethral sloughing (6/118), bladder neck contracture (2/118).

The Specialist Advisors listed the main complications as urinary incontinence, impotence, rectal injury, and fistula formation.

Literature reviews

A systematic search of MEDLINE, PREMEDLINE, EMBASE, Current Contents, PubMed, Cochrane Library and Science Citation Index was conducted using Boolean search terms, from the inception of the databases until June 2004. The York Centre for Reviews and Dissemination, Clinicaltrials.gov, National Research Register,

SIGLE, Grey Literature Reports, relevant online journals and the Internet were also searched in November 2002. Searches were conducted without language restriction.

Articles were obtained on the basis of the abstract containing safety and efficacy data in the form of randomised controlled trials (RCTs), other controlled or comparative studies, case series and case reports. Conference abstracts and manufacturers' information were included if they contained relevant safety and efficacy data. Foreign language papers were included if they contained safety and efficacy data and were considered to add substantively to the English-language evidence base. In the case of duplicate publications, the latest, most complete study was included. All identified studies were included.

List of studies found

This overview is based on seven case-series studies.

Appendix A includes a list of studies not included in the data extraction tables, but relevant to the review of this procedure.

Existing reviews on this procedure

One health technology assessment relevant to this procedure was identified [2] (Literature search date: 1998). Given the literature search date for this assessment it was decided not to incorporate the findings of this assessment into the overview.

Seven studies were included in this assessment. Of the seven studies on the use of cryosurgery as a salvage procedure in patients with recurrent prostate cancer following radiation therapy, two studies reported outcomes only, three studies reported outcomes and complications, and two studies reported only complications.

Summary of key efficacy and safety findings

Abbreviations used: PSA – prostate specific antigen; bRFS – biochemical recurrence free survival; TRUS – transrectal ultrasound

Study details	Key efficacy findings	Key safety findings	Comments
Bahn et al (2003)[3] Case series USA 59 patients March 1993–September 2001 Mean age: 67.5 years Median PSA: 5.6 (0.01–57) Selection criteria: rising PSA, men previously treated with radiation therapy with biopsy-proven recurrent prostate cancer without evidence of distant metastasis Procedure details: Patients were given a warming catheter, two freeze cycles Median follow-up: 82 months	**Outcomes reported:** biochemical-recurrence-free survival Biochemical disease free survival (PSA cut-off of 0.5 ng/ml): Overall = 59% **Stratified analysis** Preoperative PSA < 4 ng/ml = 61% Preoperative PSA 4–10 ng/ml = 62% Preoperative PSA > 10 ng/ml = 50% Gleason score 3-6 = 50% Gleason score 7 = 66% Gleason score 8-9 = 52% T stage T1-T2 = 66% T stage T3-T4 = 41% Negative biopsy = 38/38 (100%)	**Complications:** • 5 patients (8%) incontinence • 2 patients (3.4%) rectal fistula	Retrospective analysis Small patient numbers. No patients continued with adjuvant androgen deprivation after cryotherapy. Patients were considered to have a biochemical recurrence if they had an increase in PSA ≥ 0.5 ng/ml Biopsies were taken if there was a rise in PSA Authors note the two cases of rectal injury occurred during learning curve Limited information on outcomes.

Abbreviations used: PSA – prostate specific antigen; bRFS – biochemical recurrence free survival; TRUS – transrectal ultrasound

Study details	Key efficacy findings	Key safety findings	Comments
Izawa et al. (2002)[4] Case series 131 patients July 1992–Jan 1995 Follow-up: median 4.8 years (range 1.5–6.3 years) Selection criteria: biopsy proven locally recurrent prostate cancer after radiation therapy, with no clinical evidence of active metastatic disease Exclusion criteria: prior chemotherapy treatment Procedure: urethral warming catheter was used in most procedures	**Outcomes reported:** treatment failure, disease-specific survival, disease-free survival **Treatment failure:** PSA ≥ 2 ng/ml above nadir = 82/131 (63%) Positive biopsy = 23/131 (18%) Positive CT scan = 16/131 (12%) Positive bone scan = 18/131 (14%) Prostate cancer related death = 28/131 (21%) Death from other cause = 7/131 (5%) **Disease-specific survival at 5 years**: 79% overall (89% for patients treated only with radiation therapy, 50% for patients treated with hormone therapy and radiation therapy prior to cryosurgery, p < 0.00001) **Disease-free survival at 5 years**: 40% (48% for patients treated only with radiation therapy, 22% for patients treated with hormone therapy and radiation therapy prior to cryosurgery, p = 0.001)	**Complications:** None reported. Safety data previously reported by Pisters et al [(5)]	Same cohort of patients as Pisters et al [(5)] except patients excluded with prior chemotherapy. Patients were considered to have a biochemical recurrence if they had an increase in PSA ≥ 2 ng/ml Success of procedure depends on whether the cancer is androgen-dependent or androgen-independent, the PSA level prior to cryotherapy, the Gleason score for the recurrent cancer and the clinical stage before the initial radiotherapy treatment.

Abbreviations used: PSA – prostate specific antigen; bRFS – biochemical recurrence free survival; TRUS – transrectal ultrasound

Study details	Key efficacy findings	Key safety findings	Comments
Han et al (2003) [6 7] Case series 2000–2002 122 patients (18 patients undergoing salvage cryotherapy) All patients had biopsy proven prostate cancer Mean patient age was 69.7 years (53–85 years) Procedure details: Brachytherapy template, thermocouples, TRUS and urethral warmers were used Follow-up: 12 months	**Outcomes reported**: Biochemical-disease-free survival Biochemical disease free survival (PSA ≤ 0.4 ng/ml): Overall = 72% (13/18) (primary rate was 74% 66/89)	**Complications**: • 2 patients (11%) urethral sloughing • 1 patient (5.6%) urge incontinence • 2 patients (11%) incontinence • 1 patients (5.9%) penile tingling/numbness • 12 patients (86%) impotence • 1 patient (5.6%) pelvic pain • 2 patients (11%) scrotal swelling	'Third generation' cryotherapy Only a small percentage of patients received salvage cryotherapy. Complications were assessed using questionnaires. Patients were considered to have a biochemical recurrence if they had an increased in PSA ≥ 0.4ng/ml. Routine biopsies were not performed. Text and figures do not reconcile in some places.

Abbreviations used: PSA – prostate specific antigen; bRFS – biochemical recurrence free survival; TRUS – transrectal ultrasound

Study details	Key efficacy findings	Key safety findings	Comments
Chin et al. 2001[8] Canada Dec 1994–Sept 1999 118 patients (125 procedures) Selection criteria: increasing serum PSA on 3 specific determinations at least 2 years following radical radiation beam therapy with curative intent Follow up: median of 18.6 months Procedure details: urethral warming device and thermocouples were used	**Outcomes reported:** biopsy rates, biochemical recurrence. Positive biopsy cores = 23/745 (3.1%) in 7 patients. (all 7 patients underwent second cryotherapy) PSA nadir < 0.5 ng/ml = 114/118 (97%) Biochemical failure (≥ 0.5ng/ml) was in 34% of patients.	**Complications:** • 4 patients (3%) rectourethral fistula • 1 patient (1%)vesicourethral fistula beyond external sphincter • Incontinence: - 16 patients (14%) mild/moderate - 8 patients (7%) severe • 10 patients (8.5%) outlet obstruction • 6 patients (5%) debris sloughing • 2 patients (2%) bladder neck contracture	There was an 83% compliance rate for follow-up biopsy at the centre. Patients were considered to have a biochemical recurrence if they had an increased in PSA ≥ 0.5ng/ml. Complications were assessed used a non-validated questionnaire that was administered at each follow-up visit. Authors note that results indicated that any patients who underwent prior transurethral procedures were at a much higher risk for incontinence.
de la Taille et al. 2000 [9] Case series USA Oct 1994–April 1999 43 patients	**Outcomes reported:** biochemical-recurrence-free survival PSA nadir < 0.1 ng/ml = 26/43 (60%). PSA < 4 ng/ml = 16/43 (37%) PSA < 10 ng/ml = 1/43 (3%) Biochemical-recurrence-free survival (bRFS) was 79% at 6 months and 66% at 12 months	**Complications:** ▪ 11 patients (26%)rectal pain ▪ 5 patients (12%)perineum swelling/scrotal oedema ▪ 4 patients (9%) incontinence ▪ 4 patients (9%) lower tract infection ▪ 2 patients (5%) haematoma ▪ 2 patients (5%) obstruction ▪ 2 patients (5%) urinary urgency	Potential for bias: first 25 cases treated with CMS AccuProbe machine; last 18 cases treated with CryoCare Surgical System machine. Patients recruited consecutively. Patients specifically asked about incontinence at review – other complications were assessed from chart review.

Abbreviations used: PSA – prostate specific antigen; bRFS – biochemical recurrence free survival; TRUS – transrectal ultrasound

Study details	Key efficacy findings	Key safety findings	Comments
Mean age: 69.4 years (48.1–83.6 years) Mean PSA: 7.07 ng/ml (0.6–50) Selection criteria: localised recurrent prostate cancer after radiation therapy Follow-up: mean 21.9 months	bRFS of < 0.1 ng/ml group (73%) significantly greater than others (30%), p = 0.0076 8 patients had biopsies for increasing PSA levels. 3/8 had a local recurrence	▪ 2 patients (5%) urethral stricture	Incontinence was defined as one or more pads per day. Patients were considered to have a biochemical recurrence if they had an increased in PSA ≥ 0.2ng/ml or more above their PSA nadir.
Ghafar et al. 2001[10] Case series USA Oct 1997–Sept 2000 38 patients Mean age: 71.9 years (54–81.7 years) Selection criteria: clinically localised, stages T1–T3, radioresistant, recurrent prostate cancer. Follow-up: mean 20.7 months (3–37 months)	**Outcomes reported:** biochemical-recurrence-free survival 1 distant disease developed in penis bRFS was 86% at 12 months and 74% at 24 months	**Complications:** ▪ 3 patients (8%)incontinence ▪ 1 patient (3%) urinary tract infection ▪ 3 patients (8%) haematuria ▪ 15 patients (39%) perineal, rectal pain ▪ 6 patients (16%) lower urinary tract symptoms ▪ 4 patients (11%)swelling	Potential for bias: Small patient numbers. Patients recruited consecutively. Patients were considered to have a biochemical recurrence if they had an increased in PSA ≥ 0.3ng/ml or more above their PSA nadir. Incontinence was defined as one or more pads per day. Routine biopsies were not performed as part of follow-up.

Abbreviations used: PSA – prostate specific antigen; bRFS – biochemical recurrence free survival; TRUS – transrectal ultrasound

Study details	Key efficacy findings	Key safety findings	Comments
Procedure details: urethral warming device and thermocouples were used			
Pisters et al. 1997[5] USA July 1992–March 1995 150 patients (146 evaluable) Median age: 68.8 years (range 43–82 years) Selection criteria: biopsy proved locally recurrent prostate cancer with no clinical evidence of active metastatic disease Follow-up: mean 13.5 months Procedure details: single or double freeze thaw cycle, urethral warming catheter (116 patients)	**Outcomes reported:** biochemical recurrence free survival Biochemical failure = 85/146 (58%) Persistently undetectable PSA = 45/146 (31%) Detectable but stable PSA = 16/146 (11%) Negative biopsy = 85/110 (77%) Mean months to biochemical failure = 6.2 (1.4–25.8) Patients with more extensive prior therapy sig. more likely to have biochemical failure (71%) than group treated only with prior radiation (54%), p = 0.05	**Complications:** ▪ 2 patients (1%) fistula ▪ 4 patients (3%) osteitis pubis ▪ 1 patients (1%) prostatic abscess ▪ 25 (17%) obstruction requiring transurethral prostatectomy ▪ 40 (27%) obstruction requiring urethral catheterisation ▪ 73% incontinence ▪ American Urological Association symptom score < 10 = 33%; 10–20 = 38%; > 20 = 29% ▪ 18% perineal pain ▪ 72% impotence ▪ 22% any debris	Potential for bias: Unknown whether patients were recruited consecutively. Patients were considered to have a biochemical recurrence if they had an increased in PSA ≥ 0.2 ng/ml or more above their PSA nadir. Outcome measures and their validity: American Urological Association symptom score of unknown validity. Other comments: Patients were analysed in two groups, depending on whether they underwent prior radiation therapy or more extensive prior therapies, including various combinations of radiation, hormonal or chemotherapy. Complications were assessed by retrospective chart review and a mailed quality of life survey – not clear whether quality of life data reported.

Validity and generalisbaility of results

- The technology involved in this procedure is continually evolving and there have been a number of modifications to the procedure initially described in the literature, including the use of thermocouple monitoring, neoadjuvant hormonal therapy, urethral warming systems and now cryoneedles.

- As such, earlier studies may have less favourable outcomes, particularly in terms of morbidity – and later studies will have shorter-term follow-up and perhaps reflect a learning curve.

- Among the studies different definitions were used to define outcomes such as incontinence, obstruction and biochemical cure. This makes it difficult to compare outcomes across studies.

- This is particularly evident in terms of the PSA level used as an indication of a cure or a biochemical failure, where the cut-off points used in the studies ranged from 0.2–0.5 nanograms/ml.

- Many of the studies used physician records to assess complications rather than validated questionnaires. Given the interest of many of the authors in this procedure it is possible the complication rate may have been underestimated. .

- The main efficacy measure reported in the studies related to biochemical-recurrence-free survival (surrogate measure). Although biopsies were taken in some studies, not all studies reported on this outcome – making conclusions around efficacy difficult.

- Few studies reported on long-term outcomes. This is particularly important given that local recurrence and survival are outcomes of interest in relation to this procedure.

- Quality of life measures were also infrequently reported upon in the studies.

Analysis of pool literature

- The evidence for this procedure would appear to be based on uncontrolled studies.

- Studies reporting on the use of cryotherapy as primary therapy were excluded.

- Those studies in Appendix A, and excluded from the main data extraction tables, are in general those with fewer patients, reports on earlier techniques, preliminary reports on newer techniques or studies where safety and efficacy are not the main outcomes. It is unlikely that the results of these studies will add significantly to the evidence base.

- Given however the recent developments in terms of this procedure (that is, third generation) it is likely that further studies will be published in the future.

Specialist Advisors' opinions

The opinions of the Specialist Advisors were as follows.

- It is has limited application in a small number of centres.
- Would have only minor impact on the NHS as a whole.
- Main potential adverse effects of the procedure are urinary incontinence, impotence and rectal damage/fistulation.
- Cancer control is uncertain.
- Different treatment protocols are associated with different complications and success rates.
- Although outcomes following this procedure are improving due to better instrumentation, surgical technique and experience, morbidity remains high and relatively few patients have had adequate follow-up.

Issues for consideration by IPAC

None other than those described above.

References

1 Lam JS, Belldegrun AS. Salvage cryosurgery of the prostate after radiation failure. Reviews in urology 2004; 6(4):S27-S36.

2 Erlichman M, Handelsman H, Hotta SS. Cryosurgery for recurrent prostate cancer following radiation therapy. Health Technology Assessment (Rockville, Md) 1999;(13):i-v.

3 Bahn DK, Lee F, Silverman P, Bahn E, Badalament R, Kumar A et al. Salvage cryosurgery for recurrent prostate cancer after radiation therapy: a seven-year follow-up. Clinical Prostate Cancer 2003; 2(2):111-114.

4 Izawa JI, Madsen LT, Scott SM, Tran JP, McGuire EJ, Von Eschenbach AC et al. Salvage cryotherapy for recurrent prostate cancer after radiotherapy: variables affecting patient outcome. Journal of Clinical Oncology 2002; 20(11):2664-2671.

5 Pisters LL, Von Eschenbach AC, Scott SM, Swanson DA, Dinney CP, Pettaway CA et al. The efficacy and complications of salvage cryotherapy of the prostate. Journal of Urology 1997; 157(3):921-925.

6 Han KR, Belldegrun AS. Third-generation cryosurgery for primary and recurrent prostate cancer. BJU International 2004; 93(1):14-18.

7 Han KR, Cohen JK, Miller RJ, Pantuck AJ, Freitas DG, Cuevas CA et al. Treatment of organ confined prostate cancer with third generation cryosurgery: preliminary multicenter experience.[see comment]. Journal of Urology 2003; 170(4 Pt 1):1126-1130.

8 Chin JL, Pautler SE, Mouraviev V, Touma N, Moore K, Downey DB. Results of salvage cryoablation of the prostate after radiation: identifying predictors of treatment failure and complications. Journal of Urology 2001; 165(6 Pt 1):1937-1941.

9 De La TA, Hayek O, Benson MC, Bagiella E, Olsson CA, Fatal M et al. Salvage cryotherapy for recurrent prostate cancer after radiation therapy: the Columbia experience. Urology 2000; 55(1):79-84.

10 Ghafar MA, Johnson CW, De La TA, Benson MC, Bagiella E, Fatal M et al. Salvage cryotherapy using an argon based system for locally recurrent prostate cancer after radiation therapy: the Columbia experience. Journal of Urology 2001; 166(4):1333-1337.

Appendix A: Studies that met the inclusion criteria but were not tabulated.

Study title	Number of patients/ follow-up	Comments	Direction of conclusions
Anastasiadis AG, Sachdev R, Salomon L et al. Comparison of health-related quality of life and prostate-associated symptoms after primary and salvage cryotherapy for prostate cancer. *Journal of Cancer Research & Clinical Oncology* 2003; 129(12):676–82.	131 patients underwent procedure 89 primary treatment 42 radiation therapy failure	Same authors as other studies – unclear if some of the same patients. Validated questionnaires were used.	Authors note that overall QoL scores were high in both groups (no absolute numbers are given) 10% of patients incontinence 90% severe erectile dysfunction
Bales GT, Williams MJ, Sinner M et al. Short-term outcomes after cryosurgical ablation of the prostate in men with recurrent prostate carcinoma following radiation therapy. *Urology* 1995; 46(5):676–80.	23 patients 23 months	Case series. This is described as a preliminary report and the procedure described in this paper is quite different to later papers	Biopsy shows cancer at 3 months = 3/22 (14%)
Cespedes RD, Pisters LL, von Eschenbach AC et al. Long-term follow up of incontinence and obstruction after salvage cryosurgical ablation of the prostate: results in 143 patients. *Journal of Urology* 1997; 157:237–40.	143 patients Median follow-up:27 months	Case series Earlier paper of cohort in [5, 4].	See other results from later studies.
Chin JL, Touma N, Pautler SE et al. Serial histopathology results of salvage cryoablation for prostate cancer after radiation failure. *Journal of Urology* 2003; 170(4 Pt 1):1199–202.	106 patients Various follow-up	Case series. Studies specifically looks at biopsy results	A total of 818 biopsy cores were taken – a total of 23 from 15 patients were positive.
Cytron S, Paz A, Kravchick S et al. Active rectal wall protection using direct transperineal cryo-needles for histologically proven prostate adenocarcinomas. *European Urology* 2003; 44(3): 1 -3.	31 patients 12 months follow-up	Case series Preliminary report of third generation procedure.	Lower PSA levels and less rectal injury
Izawa JI, Morganstern N, Chan DM et al. Incomplete glandular ablation after salvage cryotherapy for recurrent prostate cancer after radiotherapy. *International Journal*	150 patients	Case series Looking at prognostic	Complete ablation of the prostate gland is difficult to achieve with cryotherapy.

Study title	Number of patients/ follow-up	Comments	Direction of conclusions
of Radiation Oncology, Biology, Physics 2003; 56(2):468–72.		variables	
Han KR, Belldegrun AS. Third-generation cryosurgery for primary and recurrent prostate cancer. [Review] [23 refs]. *BJU International* 2004; 93(1):14–8.	Reference made to 29 patients	Review article – limited information about patients.	Review article
Miller RJ Jr, Cohen JK, Shuman B et al. Percutaneous, transperineal cryosurgery of the prostate as salvage therapy for post radiation recurrence of adenocarcinoma. *Cancer* 1996; 77(8):1510-1514.	33 patients	Case series Report on earlier technique	Cryosurgery appears to eliminate biopsy detectable tumour.
Perrotte P, Litwin MS, McGuire EJ et al. Quality of life after salvage cryotherapy: the impact of treatment parameters.[see comment]. *Journal of Urology* 1999; 162(2):398–402.	150 patients	Case series Report on earlier technique – looks at quality of life.	Urethral warming is essential in reducing complications.
Izawa JI, Ajam K, McGuire E et al. Major surgery to manage definitively severe complications of salvage cryotherapy for prostate cancer. *Journal of Urology* 2000; 164(6):1978–81.	150 patients (analysis of 6 patients who had to undergoing surgery for complication)	Case series Same cohort in [5, 4]	In those with severe complications following cryosurgery surgery may be an option.

Appendix B: Literature search for salvage cryotherapy

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in EMBASE, Current Contents, PredMedline and all EMB databases.

For all other databases a simple search strategy using the key words in the title was employed.

#	Search History
1	exp CRYOSURGERY/
2	exp CRYOTHERAPY/
3	(salvage adj2 cryo$).tw.
4	exp Salvage Therapy/
5	1 or 2
6	4 and 5
7	exp Prostatic Neoplasms/
8	exp Neoplasm Recurrence, Local/
9	7 and 8
10	cryo$.tw.
11	9 and 10
12	(cryo$ adj2 prostate).ti.
13	7 or 8
14	3 or 6
15	13 and 14
16	11 or 12 or 15
17	limit 16 to human