Early oncological and functional outcomes following radical treatment of high-risk prostate cancer in men older than 70 years

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Early oncological and functional outcomes following radical treatment of high risk prostate cancer in men more than 70 years of age: A prospective longitudinal study

Running head: Radical treatment of high risk prostate cancer in men more than 70 years

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None to declare.

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Abstract

Background:

Assess early oncological and functional outcomes following radical treatment of men with high risk prostate cancer and aged more than 70 years.

Patients and Methods:

335 men with high risk prostate cancer (PSA ≥20 ng/ml or biopsy Gleason score 8–10 or ≥cT2c) received radical treatment between 2007 and 2014. Men were identified from comprehensive clinical databases hosted at a tertiary cancer centre in the UK. The data included basic demographics, and follow-up on functional and oncological outcomes using validated patient reported outcome questionnaires. Univariate and multivariate analyses were performed in SPSS version 21.

Results:

117 patients received radical radiotherapy alone, 167 received neo-adjuvant hormone therapy and radiotherapy, and 54 radical prostatectomy with extended lymph node dissection. Mean age was 72.8, SD 2.1 with a mean follow-up of 40.9 months, SD 25.5 months. Of the patients who underwent LRP 24 (44.4%) had positive surgical margins, mean lymph nodes dissected were 18.7, SD 6.7 (min 15 and max 33). Five men experience post-operative complications in the form of pseudoaneurism of internal iliac branch, leg ischemia, high Co2 retention, and two men experienced sepsis. Incidence of biochemical recurrence was significantly lower 16.7% in the surgery group, compared to RT 51.3% and RT and HT 30.5%, Kaplan-Meier analysis $P<0.001$ over 3 years of follow-up

Conclusion

Radical surgery with extended lymph nodes dissection appears to have good short-term oncological and functional outcomes compared to radiotherapy with or without hormones in high risk men over 70 years. Based on these findings treatment decisions should be individualised and after considering the health status of each patient.

Introduction

Prostate cancer remains the most common malignancy among elderly men and is the second leading malignancy in the Western World [5] with steadily increasing incidence over the last decade.

Between 2000 and 2050, the number of elderly men affected by prostate cancer is expected to increase 4-fold worldwide [5]. All this leads to a healthcare challenge in terms of radical treatment, in particular surgery in elderly men with good performance status. Current practice of radical treatment for localized prostate cancer is guided by expert guidelines, recommending potentially curative therapy for whose with life expectancy of at least 10 years [1, 2]. Guidelines also stipulate men with limited life expectancy are more likely to die from health conditions other than prostate cancer, and are best managed conservatively as radical treatment may impair their quality of life. This approach may deprive survival advantage in men older than 70 years, especially with good performance status [3]. This is increasingly realized in the presence of minimally invasive surgery (laparoscopic prostatectomy [LRP], with or without assistance of robot), with demonstrated improved perioperative morbidity and outcomes [4]. Thus, accepted 10-year rule- a common practice among urologists and radiation oncologists may need a re-visiting [6, 7]. However, aging is a highly individualized, multidimensional process where chronologic age does not always predict the physiologic decline in an individual because, in part, of the effect of comorbidity [9]. Bearing this in mind, there is a need for an approach to extend indications of surgical treatment in selected group of men more than 70 years of age.

Evidence from a recent study suggests that in age-stratified random sample of 347 men from a cohort of patients with newly diagnosed prostate cancer in the Ontario Cancer Registry, several clinical factors can influence treatment options [6]. Patients who were younger than 60 years were more likely to receive radical prostatectomy than radiation therapy or no therapy. Men between 60 and 69 years of age were more likely to receive radiation therapy than radical prostatectomy. Men between 70 and 79 years were most likely to receive conservative therapy such as hormone therapy, and nearly all men over 80 years received no therapy. The decreased likelihood of receiving curative therapy is correlated with patient age, Charlson index score and tumor stage [6].

The above observation is further supported by reported literature from others. Older men have been shown to receive potentially curative therapy (radical prostatectomy or radiotherapy) less often than younger men. Radical prostatectomy is preferred treatment in men younger than 70 years, whereas radiation therapy is applied predominantly in patients older than 70 years [6-8]. Conservative therapy such as watchful waiting or androgen deprivation by luteinizing hormone-releasing hormone analogs is preferentially applied in men older than 80 years.

However, a judicious decisions needs to be made considering age, clinical stage, PSA level, histological grade, and comorbidities. These should be carefully balanced against the survival advantage before making a treatment decision [8].

In our centre, we have been offering radical surgery in high risk patients (PSA ≥ 20; Gleason score ≥ 8 and more, ≥cT2c disease) based on a careful assessment and discussions in tumour boards (multidisciplinary teams). We aim to compare the oncological and functional outcomes in elderly men over 70 years diagnosed with high-risk prostate cancer treated with radical therapy (surgery and radiotherapy).

Patients and Methods

The study had Caldecott Institutional Approval (Caldicott/CSAppGN021211). During January 2007 and December 2014, 335 patients who underwent radical radiotherapy, neoadjuvant hormonal therapy and radiotherapy, or laparoscopic radical prostatectomy identified from comprehensive clinical databases hosted at a tertiary cancer centre in the UK. For this study, radiotherapy with or without hormone included men up to December 2011 to get a meaningful follow-up of at least 3 years for each man. For surgery, each patient had at least one year follow-up to provide a meaningful early oncological and functional outcomes

The TUCAN (Tayside Urological Cancers Network Database) collects routine data from the population of urological cancers in Tayside, Scotland. NHS Tayside serves a predominantly Caucasian rural and urban population of more than 405,721 based on mid-year 2011 population estimates published by the General Register Office for Scotland. Population is registered with health care board through a unique number called as Community Health Index number (CHI number) and is served by 75 general practices and single tertiary urological cancers services. All newly diagnosed cancers are reviewed by a local multidisciplinary team and the meeting records are stored in a database known as the "Tayside Urological Cancer Network Database" [9]. Study data was collected using a validated record-linkage methodology using the CHI number as described by us previously [10, 11].

Record linkage technique brings together two or more records relating to the same individual identified by a common identifier (Community Health Index [CHI] number in this series). Cross-linkage of databases enabled demographical and clinical data to be securely managed at one centralized database for the purpose of this study.

The database with (CHI) was linked to the following clinical systems:

(i) WISDOM oncology system (Web Information System For Data Oncology Management) which securely stores the following clinical information: clinical presentation, PSA, cancer stage, Gleason score, radiotherapy, clinical complications, follow-up and mortality

(ii) Referral Management System (RMS) which is a primary care system for a population of more than 400,000 individuals. Data linkage captured co-morbidities

(iii) Multidisciplinary Board Meeting (MDT) records where all men diagnosed with prostate cancer are discussed on a weekly basis.

(iv) Integrated Clinical Environment (ICE) system provides clinicians with diagnostic services as a means to electronically order tests and view results. Using the CHI number, we searched for sequential PSA results.

(v) Records were searched using Clinical Portal and the In House Surgical Information System web and Technology (Insite), these databases host secure electronic patient records which systematically captures follow-up history including communication between acute and primary care.

Inclusion criteria were: (1) patients more than 70 years of age who were newly diagnosed and histologically confirmed localized or locally advanced adenocarcinoma of prostate; (2) patients suitable and those opting for primary radical radiotherapy, neoadjuvant/adjuvant hormonal therapy for 24 months and radiotherapy or radical prostatectomy; (3) patients ≥ age of 70 years with one of the following high risk factors, (PSA ≥20 ng/ml or biopsy Gleason score 8–10 or ≥cT2c). Exclusion criteria were: (1) Patients who would not have qualified for radical surgical treatment and radiotherapy with hormones was considered as the only option after multidisciplinary meeting discussion (this group invariably included men with PSA more than 50 or MRI showing gross extracapsular extension precluding any safe resection if they had opted for surgery) 2) patients with missing clinical data such as dose of radiotherapy, tumour stage, Gleason score, PSA or no history of follow-up 3) patients unable to meet the inclusion criteria.

All LRP at our institution were performed by one surgeon (GN). Extended pelvic lymphadenectomy was performed on all patients as described before [12]. All pathological RP specimens were reviewed by a senior Consultant Uropathologists (SL) and discussed in multidisciplinary team meetings to record proper staging including discussion of adjuvant treatment (radiotherapy or hormones)

Demographic and clinical data were collected prospectively from consecutive patients and entered into a comprehensive electronic database such as our (Integrated Clinical Environment). Variables included the following: age, PSA before treatment, PSA post-treatment, cancer stage, Gleason score, and co-morbidities.

Oncological outcomes

The primary outcome was the incidence of biochemical recurrence. This was defined as detectable PSA (>0.2 ug/L) in at least 2 consecutive measurements for men treated by LRP [13]. After primary

radical radiotherapy or neoadjuvant hormonal treatment and radiotherapy biochemical recurrence was defined as a consecutive PSA increase > 2 ng/mL higher than the PSA nadir value [13]. Positive surgical margins and the need for adjuvant treatment were recorded. Secondary outcomes being functional outcome and perioperative morbidity.

Functional outcomes

Radiation induced proctitis was graded according the European Organization for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) grading system of radiation proctitis [14] (Table 1). The grading classification was used by two members of the research team (AA and CP) to rate the severity of proctitis for each patient within the study. Inter-rater reliability was assessed using the Kappa statistic (Kappa=0.809 with $p<0.001$) and was found to have substantial agreement [15].

LRP patients were given the self-administered International Consultation Incontinence Questionnaire (ICIQ-UI, see supplementary information for questionnaire) [16] at 3, 6, 9 and 12 months post-surgery. For the purpose of this study *continence* is defined as using no pad or a safety pad [17] in a 24 hour period.

Statistical Analysis

Data were double-entered into the Statistical Package for Social Sciences (SPSS, version 21). Pearson product moment correlation coefficients, paired sample t-tests, Chi-squared, Kruskal-Wallis H test, and Mann-Whitney U test were used. Biochemical recurrence rates were obtained by using the principles of Kaplan-Meier analysis, the Log-Rank, Breslow and the Tarone-Ware tests. Statistical significance was defined as $p<0.05$.

RESULTS

Of the 338 patients, 117 were treated with radical radiotherapy alone, 167 received neo-adjuvant hormone therapy and radiotherapy, and 54 LRP (Table 2). The overall mean age was 72.8 ± 2.1 with a mean follow-up of 40.9 months, SD 25.5 months, max 96 months. There was a statistically significant difference in the mean age among the three groups F(2, 332)=6.889, p=0.001, RT 73.2, SD2.2, RT and HT 72.7, SD 2.0 and LRP 72.2, SD1.8, but the age ranges (70 -77 years) were the same for all three treatment groups. The distribution of clinical characteristics across the treatment modalities are detailed in Table 2. In particular RT <T3 was found in 88, 29 ≥T3, Gleason 6 (31), Gleason 7 (47), Gleason 8-10 (39); RT and HT <T3 (78) and ≥T3 (89), Gleason 6 (22), Gleason 7 (32) and Gleason 8-10 (113), and LRP cT3 (47) and >T3 (7), Gleason 6 (8), Gleason 7 (8) and Gleason 8-10 (38). There was no statistically significant difference in the mean PSA levels before radical treatment across the treatment modalities in the cohort.

Of the patients who underwent LRP 24 (44.4%) had positive surgical margins, 39 (76.5%) has extended PLND with mean of 18.7, SD 6.7 (min 15 and max 33) lymph nodes, see Table 3. Remaining had limited lymph node dissection. Two men had positive nodal disease and required hormonal treatment. PSA remain undetectable in both the men. Seven men required salvage radiotherapy following surgery and biochemical recurrences. Four of these have undetectable PSA at last follow-up. Five men experience post-operative complications in the form of pseudoaneurysm of the internal iliac artery (Figure 1), leg ischemia, high Co2 retention, and two men experienced sepsis. The majority of men stayed in hospital for two nights post LRP and 91% of men were continent by 12 months post-surgery. Two patients had rectal injury; which was identified and repaired during the surgery (histopathology of one patient with rectal mucosa removed with the prostatic specimen, see Figure 2). Following RT alone 47 (40.2%) of men did not experience proctitis, Grade 1 was reported in 53 (45.3%), and ≥Grade 2 14 (14.6%). For those men treated by HT and RT 68 (40.7%) did not report proctitis, Grade 1 66 (39.5%) and ≥Grade 2 33 (19.8%).

There was a significant difference in the PSA level between the treatment modalities H(2) = 116.6 , p<.001. A bonferroni correction was applied and so all effects are reported at a .0167 level of significance. PSA levels following radical treatment was significantly lower for men treated by LRP (U = 39.5, p<.000) when compared to RT and RT and HT. However, PSA levels following radical treatment was significantly lower for men treated with RT and HT (U = 8575, p= .011) compared to RT alone, see Figure 3. The results from the cox proportional hazard analyses $\chi^2(6) = 833.7$, $p < .003$, identified the following factors to have a beneficial association with biochemical recurrence following radical treatment in men over 70 years old: baseline age (.917 p=.029), Gleason score 6

(.357, p=.005), Gleason score 7 (.584, p=.0.31), however radiotherapy alone (1.977, p=.007) demonstrated negative association with the incidence of biochemical recurrence in this patient population, see Table 2.

The log rank test was performed to determine if there were differences in the biochemical recurrence distribution among the three groups: RT, RT and HT and LRP modalities. The biochemical recurrence distributions for the three groups were statistically significantly different, $\chi^2(2) = 21.567$, p=0.000 (Figure 2).

Discussion

The current study set out to compare the early oncological and functional outcomes in elderly men over 70 years diagnosed with high-risk prostate cancer treated with radical therapy. This study has several important findings. First, LRP with extended lymph node dissection is feasible and acceptable in elderly (≥70years) men with high risk prostate cancer. Evidence acknowledges that elderly men opting for LRP are more likely to have high risk tumour and advanced pathological stages, thus justifying a more aggressive approach in this patient population [18]. Those with biochemical recurrences could potentially be offered salvage treatment options, although numbers are small.

In contemporary practice, however, few men aged 70 years or older undergo curative therapy for high-risk prostate cancer. Compared with observation alone, curative treatment (surgery or radiation therapy) has been shown to improve survival in men aged 65–80 years with low- or intermediate-risk prostate cancer (Gleason score <7) [19]. However, in their retrospective series high-risk patients were not included in the analysis but data acknowledges that men older than 70 years may benefit from curative therapy who have high risk disease prostate cancer [18].

In high-risk prostate cancer, radical prostatectomy has been effective in oncological control. A large number of patients are cured with surgery alone. Data from a study of biochemical recurrence-free survival showed that 40% of patients had no evidence of disease 10 years after surgery for high-risk cancer [20, 21]. To date, we don't have trial data comparing radical prostatectomy with radiation therapy, so no formal conclusions can be drawn, or indeed the overall benefits for senior men over 70 years with high risk prostate cancer remains little known [22]. But here, we present the first study which compares the incidence of biochemical recurrence across three treatment modalities in high risk prostate cancer in older men. Our findings identify the overall incidence of biochemical recurrence was low 16.7% in the LRP group, compared to RT 51.3% and RT and HT 30.5%, Kaplan-Meier analysis P<0.000 over a 3 years of follow-up. Follow-up, however remains short and it would be interesting to find out long-term outcome of this cohort.

Radiotherapy is standard treatment for localised prostate cancer and is often combined with hormone treatment to prevent androgen stimulation of prostate cancer. Hormone therapy carries significant morbidity [23] and can only be justified in the radical treatment of localized disease if it can be balanced against a significant gain in disease control and survival. A recent systematic review [24] outlines evidence that the use of combined treatment of androgen deprivation therapy and radiotherapy for intermediate and high-risk localised and locally advanced prostate cancer.

Noteworthy, the patients in our series who underwent RT treatment alone had the underpinning clinical rationale for this practice as the evidence to support the usage of combination of HT and RT was still in its infancy, at that time. However, our findings are in keeping with favorable outcome following the usage of combination HT and RT versus RT alone, based on the findings of the incidence biochemical recurrence over time [24]. In clinical practice the optimal timing, duration, formulation and the management of side-effects of combination HT and RT remain important questions for further research [24]

We acknowledge that using the ICIQ-UI evaluation is the gold standard for evaluating patient's health status [25] and controlling for variations in surgical ability and skill [26] was a strength to this study's methodology. The mean duration of hospital stay was 2 days (1-35 days) and similar to other centres [27, 28]. Using the continence definition of 0-1 pads our data showed that LRP can offer good functional outcome with approximately 91% of men returning to baseline continence function by 12 months, and this is similar to data published elsewhere [29]. In contrast, in a prospective study of LRP at 1 year identified that only 60% of men were continent [26].

The primary goal of radical prostatectomy is cancer control or eradication for patient survival. Prediction of LRP long-term oncological outcomes are linked to many established clinical factors: preoperative prostate specific antigen (PSA), clinical and pathologic staging, Gleason grade, seminal vesicle invasion, lymph node invasion, and positive surgical margins [30]. Our study has demonstrated good oncological outcome in this patient group with 84.8% biochemical recurrence-free survival at 37 months comparable with existing data [31].

The single-surgeon design is advantageous to the study methodology as all of the patients received the same postoperative care and counselling. This allowed for a more critical comparison of oncological and functional outcomes following LRP over time. Furthermore, the data in our study was gathered prospectively by third party and assessed without involvement of surgeon to avoid recall and reporting bias. A further strength to this study was the use of a validated standardised questionnaire, the ICIQ-UI, where by other available studies have used interviews or non-validated questionnaires [32, 33]. There are several limitations to our prospective longitudinal observational study. We did not use validated questionnaires to assess erectile dysfunction as most of these men opted for wide local excision in view of high risk disease or for radical radiotherapy with hormones. Moreover, there is a lack of randomization to treatment allocation which may introduce selection bias, however study represents a more of "real life" clinical practice. Finally, we acknowledge that the results should be replicated in a larger sample size with a longer follow-up duration. Despite

these limitations, the results provide new emergent information to inform the clinical management of elderly men with high risk prostate cancer.

Conclusion

High risk prostate cancer treated by radical surgery demonstrated improved early oncological and functional outcomes compared to radiotherapy with or without hormones. Radical prostatectomy was safe and feasible with good functional outcome, and these findings should inform future treatment decisions in men aged more than 70 years with high risk disease and good performance status.

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Table 1: Grades of proctitis

Grade	Sign and symptoms	Overall management
0	No symptoms	Does not require medication
1	Minimal side effect such as urgency, occasional pain, superficial ulceration , < 1cm^2, mild stricture and occult rectal bleeding	Treated as outpatient and does not require lifestyle adjustments.
2	Intermittent urgency and pain, superficial ulceration >1cm^2, intermittent rectal bleeding and moderate stricture	Treated as outpatient and requires lifestyle adjustments.
3	Persistent urgency, pain and bleeding, deep ulceration associated with sever stricture	Needs hospital admission or minor surgical intervention associated radical adjustment of the lifestyle
4	Sever urgency associated with sever uncontrollable pain, sever bleeding, perforation, fistula and complete obstruction	Needs hospital admission or major surgical intervention
5	Multi-organ failure, sepsis and death	Fatal side effects

Table 2 Distribution of clinical and demographic characteristics

Baseline Clinical and Demographic Variables	RT (n117, 34.9%)	RT + HT (n167, 49.9%)	LRP (n54, 15.2%)	p Value
Age	73.3, SD 2.2 (min 70 max 77)	72.7, SD 2.0 (min 70 max 77)	72.2, SD 1.8, min 70 max 77)	F(2, 335)=6.889, p=0.001
Cancer Stage				
T2a	14 (12.0%)	10 (6%)	10 (18.5%)	X^2 (2, N = 335) =26.82, p=0.000
T2b	74 (63.2%)	0 (0%)	10 (18.5%)	
T2c	0 (0%)	68 (40.7%)	27 (50%)	
T3a	27 (23.1%)	10 (6%)	7 (13%)	
T3b	2 (1.7%)	78 (46.7%)	0	
T4	0 (0%)	1 (0.6%)	0	
Gleason score				
2-6	31 (26.5%)	22 (13.2%)	8 (15.7%)	X^2 (4, N = 335) =38.35, p=0.000
7	47 (40.2%)	32 (19.2%)	8 (15.7%)	
8-10	39 (32.5%)	113 (67.7%)	38 (68.6%)	
PSA Before Treatment	13.01, SD 6.8 (min 1.2 max 31.9)	12.8, SD 7.6 (min 1.3 max 32.0)	10.7, SD 5.3 (min 4.5 max 33.0)	F(2, 335)=2.140 p=0.119
PSA After Treatment	2.5, SD 4.2 (min LT0.1 max 25.4)	2.4, SD 4.0 (min LT 0.1 max 24.2)	0.04, SD 0.1 (min LT0.1 – max 1.0)	F(2, 335)=9.030 ,p=0.000
Number co-morbidities				
0	69 (59.0%)	100 (59.9%)	20 (37.0%)	X^2 (4, N = 335) =34.37, p=0.000
1	35 (29.9%)	53 (31.7%)	14 (26.0%)	
2 or more co-morbidities	13 (11.1%)	14 (8.4%)	20 (37.0%)	

Table 3 Cox proportional hazard analysis for factors that influence biochemical recurrence in men over 70 years treated by radical treatment.

Variables	Categories	P Value	Hazard Ratio	(95 % confidence interval)
Age	In years	.029*	. 917*	.849-.991*
Gleason Score	Gleason score 6	.005**	.357**	.173-736**
	Gleason score 7	.031*	.584*	.358-952*
Radical treatment	Radiotherapy	.007**	1.977**	1.203-3.249**
	Laparoscopic radical prostatectomy	.520	1.331	.557-3.180
Number of Co-morbid conditions	Continuous	.376	1.156	.839-1.593

**Significant at the 0.01 level, * Significant at the 0.05 level

Table 4 Clinical and functional outcomes

Treatment modality and clinical outcomes		n (%)
Radical Surgery		
Positive surgical margins	Yes	24 (44.4%)
	No	30 (55.6%)
Pelvic lymph node dissection	Yes	39 (76.5%)
18.7, SD 6.7 (min 15 and max 33)	No	12 (23.5%)
Continence rates at 1 year post LRP	0-1 Pads	46 (91.0%)
	2>pads	8 (9.0%)
Post-operative complications	None	49 (90.7%)
	Haematoma	1 (1.9%)
	Leg ischemia	1 (1.9%)
	High Co2 retention	1 (1.9%)
	Sepsis	2 (3.7%)
Number of days in hospital	Two	29 (53.7%)
	Three	17 (31.5%)
	Four	4 (7.4%)
	Five	2 (3.7%)
	>1 week	2 (3.8%)
Incidence of biochemical recurrence	Yes	9 (16.7%)
	No	45 (83.3%)
RT		
Grade of proctitis	Grade 0	47(40.2%)
	Grade 1	53 (45.3%)
	Grade 2	11 (11.1%)
	Grade 3	2 (2.6%)
	Grade 4	1 (.9%)
Incidence of biochemical recurrence	Yes	60 (51.3%)
	No	57 (48.7%)
RT and HT		
Grade of proctitis	Grade 0	68 (40.7%)
	Grade 1	66 (39.5%)
	Grade 2	23 (13.8)
	Grade 3	7 (4.2%)
	Grade 4	3 (1.8%)
Incidence of biochemical recurrence	Yes	51 (30.5%)
	No	116 (69.5%)

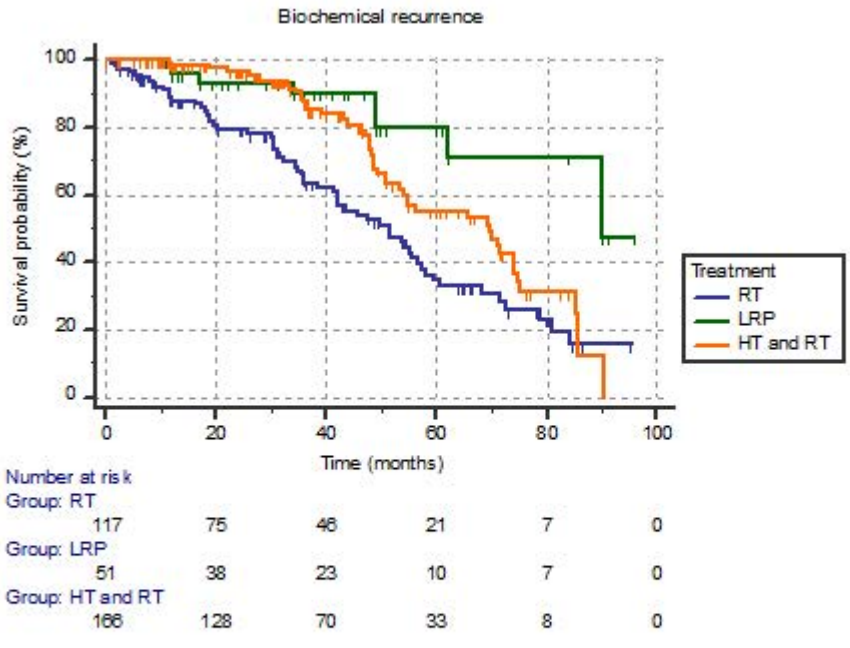

Figure 3. Kaplan-Meier analysis of biochemical relapse over time by treatment modality