High- Vs. Low-Dose Radio-Iodine Therapy for Initial Thyroid Remnant Ablation in Post-Thyroidectomized Patients with Non-Metastatic Differentiated Thyroid Cancer: A Meta-Analysis

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ABSTRACT

The use of high- or low-dose radio-iodine therapy (RAIT) for initial thyroid remnant ablation in post-thyroidectomised patients diagnosed with differentiated thyroid cancer (DTC) with no distant metastases has long been a subject of much debate. Meta-analyses and systematic reviews have been previously made using both randomised control trials (RCTs) and observational studies without due regard to differences in study design. Hence, a more focused meta-analysis of available RCTs alone was conducted to determine the presence of a compelling difference between the initial remnant ablation success rates of high- and low-dose RAIT in post-thyroidectomised DTC patient without distant metastases. An extensive search of PubMed and Cochrane Central register of RCTs (up to August 2013) was performed by two reviewers, which was completed by hand search of references from relevant articles and review papers published from 1996 to 2012. The two reviewers independently selected eligible studies, with disagreement resolved by consensus. The inclusion criteria were as follows: (a) randomised controlled trials, (b) post-thyroidectomised adult subjects diagnosed with well differentiated thyroid cancer and no evidence of distant metastases, and (c) subject randomisation into 30–50 mCi or 100 mCi ^{131}I treatment groups. Studies were excluded if (a) the full text of the study is not available, (b) the study is in another language other than English, and (c) if the data on relative risk was not available or could not be derived from the study. Of eight published RCTs on radio-iodine therapy as of August 2013, only 5 were eligible for this meta-analysis; namely those by Johansen et al. (1991), Bal et al. (1996), Zaman et al. (2006), Mäenpää et al. (2008) and Caglar et al. (2012). The same two reviewers independently extracted data from the full text of the selected five studies. Two-by-two tables comparing frequencies of successful and failed remnant ablation using low-dose (30–60 mCi) and high-dose (~100 mCi) RAIT were derived from the published results of the included studies, and the weighted and pooled relative risks for successful remnant ablation were computed via the Mantel-Haenszel method using a fixed effects model (α = 5%). Subgroup analyses were performed based on different definitions of a successful remnant ablation. The pooled relative risk (–0.03) was statistically insignificant (p = 0.54) and had poor precision (95% confidence interval of [–0.12,0.06]) even when adjustments to the varied definitions of a successful ablation were performed. Thus, using available RCTs that compare high- and low-dose RAIT for remnant ablation of DTC, there is an apparent trend favouring higher success rates using high-dose RAIT. However, the lack of well designed RCTs precludes recommending high-dose initial RAI ablation, and encourages the present practice of individualized

Keywords: *RAI therapy, radioactive iodine ablation, non-metastatic, well-differentiated thyroid cancer, meta-analysis*

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INTRODUCTION

The use of radioactive iodine (RAI) ablation of thyroid tissue remnants after near or total thyroidectomy in patients diagnosed with differentiated thyroid cancer (DTC) is generally considered part of standard medical care in high-risk and select low-risk patients (1–3). In their 2009 revised guidelines, the American Thyroid Association recommends the use of the first dose of RAI after thyroidectomy in selected DTC patients for remnant ablation, adjuvant therapy or RAI therapy (4). This has been shown to reduce the rates of disease recurrence, distant metastases and mortality (5–7). However, just how much radio-iodine is to be given initially has been the subject of much debate. Advocates of high and low doses of radio-iodine each have their opinions on the matter backed up by their own armament of research studies, most of which are retrospective and observational in nature. Due to the sensitive nature of the problem, only a handful have ventured into conducting randomized controlled trials (RCTs) that aimed to look at the differences in the success rates of high- and low-dose RAI therapies on the initial ablation of thyroid tissue remnants. Despite the effort, these RCTs turned out to have conflicting results that did not really help in resolving the question at hand.

In an attempt to arrive at a cohesive conclusion from all the research that has been done on which RAIT approach is superior, meta-analyses have been conducted by several authors previously.

Sawka et al. (8) made use of cohort studies to determine the overall effectiveness of RAI therapy in well differentiated DTC. Based on the limitations of the studies that they employed in their analysis, they were not able to recommend an optimal dose for successful RAI remnant ablation. Doi et al. (9) concluded that high-dose RAI therapy is more effective in successful ablation despite using studies of different designs (i.e., RCTs and cohort studies). Cheng et al. claimed that there is no significant difference in the rate of successful ablation using 1100 MBq and 3700 MBq of ^{131}I after analyzing published RCTs (10).

Thus, the conclusiveness of published meta-analyses on the topic of high- vs. low-dose RAIT remains unsettled. In this light, this meta-analysis aims to shed light on what can truly be concluded from RCTs done on the effectiveness of high- and low-dose RAITs.

METHODOLOGY

An extensive search of PubMed and Cochrane Central register of randomized clinical trials (RCTs) published up to August 2013 was performed by two reviewers (JM and IB). The following key words were used to screen the PubMed and Cochrane databases: ("randomised controlled trial" OR "RCT") AND ("Radio-iodine ablation" OR "Radio-iodine therapy") AND ("well differentiated thyroid cancer" OR "papillary thyroid cancer" OR "follicular thyroid cancer"). This was completed by hand search of references from relevant articles and review papers published from 1996 to 2012.

The two reviewers (JM and IB) independently selected eligible studies, with disagreement resolved by consensus. The inclusion criteria were as follows: (a) randomised controlled trials, (b) post-thyroidectomised adult subjects diagnosed with well differentiated thyroid cancer and no evidence of distant metastases, and (c) subject randomisation into 30–50 mCi or 100 mCi ^{131}I treatment groups. Studies were excluded if (a) the full text of the study is not available, (b) the study is in another language other than English, and (c) if the data on relative risk was not available or could not be derived from the study.

The same two reviewers independently extracted data from the full text of the selected studies. Critical appraisal of the eligible studies was done to assess for bias. A chi-squared test of heterogeneity was performed to determine the consistency of the results of the studies included in this meta-analysis. Two-by-two tables comparing frequencies of successful and failed remnant ablation using low-dose (30–60 mCi) and high-dose (~100 mCi) RAIT were derived from the published results of the included studies. Using Review Manager (RevMan) software version 5.2.6, weighted and pooled relative risks for successful remnant ablation were computed via the Mantel-Haenszel method using a fixed effects model (α = 5%). Subgroup analyses were performed based on different definitions of a successful remnant ablation. No other clinical outcome was analysed since only one of the eligible articles reported other clinical parameters of RAI therapy (e.g., adverse effects).

RESULTS AND DISCUSSION

Seven published randomized controlled trials satisfied the inclusion criteria. These were by Creutzig (11), Johansen et al. (12), Bal et al. (13), Zaman et al. (14), Mäenpää et al. (15), Kukulska et al. (16) and Caglar et al. (17). However, critical appraisal of these articles led to the exclusion of the studies by Creutzig and Kukulska et al. since the data on the success rate of initial thyroid remnant ablation using high- and low-dose RAI therapy cannot be extracted from the published figures.

Table 1 shows a summary of the selected RCTs for this meta-analysis. All of the eligible studies had patients with differentiated thyroid cancer without any evidence of metastasis after total or near total (subtotal) thyroidectomy. Evaluation of the success of remnant ablation was done as early as 3 months to as late as a year after RAI administration.

All of the five selected studies employed follow-up whole body ^{131}I scintigraphy and serum thyroglobulin (Tg) to determine the presence of iodine-avid thyroid tissue remnants after radio-iodine ablation. Only the study by Caglar et al. used neck sonography to

Table 1. Summary of sample size, thyroid cancer histology, type of thyroid surgery, post-operative TNM stage, and follow-up schedule after radio-iodine ablation therapy used in the five selected studies.

Author	N	Histology	Surgery	Staging	Follow-up Schedule
Johansen et al.	63	DTC[a] (specific type not reported)	TT[d] or STT[e]	Tx N0 M0	3 to 4 months
Bal et al.	149	DTC (specific type not reported)	TT or NTT[f]	Tx N0 M0	6 months to 1 year
Zaman et al.	40	PTC[b], FTC[c]	TT or NTT	Tx N0 M0	6 months
Mäenpää, et al.	158	PTC, FTC	TT or NTT	Tx N0 M0	4 to 8 months
Caglar et al.	108	PTC, FTC	TT	Tx N0 M0	6 months

[a]differentiated thyroid carcinoma, [b]papillary thyroid carcinoma, [c]follicular thyroid carcinoma, [d]total thyroidectomy, [e]subtotal thyroidectomy, [f]near total thyroidectomy

determine any residual tissues. Table 2 summarizes the definitions of successful remnant ablation after initial RAI therapy used by the selected studies.

Further evaluation of the remaining five studies revealed that only the study by Mäenpää et al. had valid results (i.e., power of 0.80, 5% confidence

Table 2. Summary of operative definitions of a successful remnant radio-iodine ablation used in the selected five studies.

Author	Operative Definitions of A Successful Remnant Ablation
Johansen et al.	absence of pathologic 24-h RAIU (1073 MBq) or 72-h RAIU (3700 MBq) in the neck (pinhole) and whole body (planar) scans + serum Tg < 5 ng/mL
Bal et al.	absence of thyroid bed activity in a 5 mCi diagnostic whole body scan 131I neck scan at 48 hours + neck uptake of <0.2% of the administered activity + serum Tg<10 ng/mL
Zaman et al.	negative whole body 131I scintigraphy + serum Tg <2 ng/mL
Mäenpää, et al.	negative whole body 131I scintigraphy + serum Tg < 1 ng/mL + absence of palpable neck masses
Caglar et al.	(a) strict criteria based on three tests: (i) negative neck ultrasound (ii) no tracer uptake or < 2x background activity in diagnostic whole body 131I scintigraphy or ≤ 0.2% RAIU (iii) serum Tg < 0.2 ng/mL (b) strict criteria based on two tests: (i) negative neck ultrasound (ii) serum Tg < 0.2 ng/mL (c) lax criteria based on three tests: (i) negative neck ultrasound (ii) no tracer uptake or < 2x background activity in diagnostic whole body 131I scintigraphy or ≤ 0.2% RAIU (iii) serum Tg < 2 ng/ml (d) lax criteria based on two tests: (i) negative neck ultrasound (ii) serum Tg < 2 ng/mL

level) and clinically important and relevant recommendations. The rest of the remaining studies all had low power (i.e., 0.27 for Bal et al., 0.25 for Caglar et al., 0.12 for Johansen et al., and 0.24 for Zaman et al.) and unclear patient randomization. No evident significant risk of bias was found in all of the five included studies.

The individual results of Bal et al., Zaman et al., and Mäenpää et al. showed an increase in the rate of successful remnant ablation (from 1.16% after low-dose RAI therapy to 20% after high-dose RAI therapy), while those of Johansen et al. and Caglar et al. demonstrated otherwise. Using the results of the strict criteria for three tests by Caglar et al. alongside the rest of the included studies, the pooled risk difference is –0.05, barely favouring the use of high-dose RAI ablation therapy (Fig. 1). This is statistically insignificant (p = 0.31) and has low precision (95% confidence interval of [–0.14,0.04]). The results were similar when the strict criteria for two tests or the lax criteria for both three and two tests by Caglar et al. were used (Appendix A).

Furthermore, the pooled risk difference remained statistically insignificant and had low precision even when adjustment to the criteria used to define a successful ablation was made (Appendix B).

If deference is made to the prevalent local practice of using a serum Tg level of < 2 ng/mL as a cut-off value in conjunction with a negative WBS to define successful ablation, a statistically insignificant pooled risk difference (–0.08, p = 0.25) is obtained using

Study or Subgroup	Low-dose RAIT Events	Low-dose RAIT Total	High-dose RAIT Events	High-dose RAIT Total	Weight	Risk Difference M-H, Fixed, 95% CI
Bal 1996	17	27	28	38	14.7%	-0.11 [-0.34, 0.12]
Caglar 2012	32	53	35	55	25.1%	-0.03 [-0.22, 0.15]
Johansen 1991	21	36	14	27	14.3%	0.06 [-0.18, 0.31]
Mäenpaä 2008	42	81	43	77	36.7%	-0.04 [-0.20, 0.12]
Zaman 2006	8	20	12	20	9.3%	-0.20 [-0.50, 0.10]
Total (95% CI)		**217**		**217**	**100.0%**	**-0.05 [-0.14, 0.04]**
Total events	120		132			
Heterogeneity: Chi² = 2.05, df = 4 (P = 0.73); I² = 0%						
Test for overall effect: Z = 1.01 (P = 0.31)						

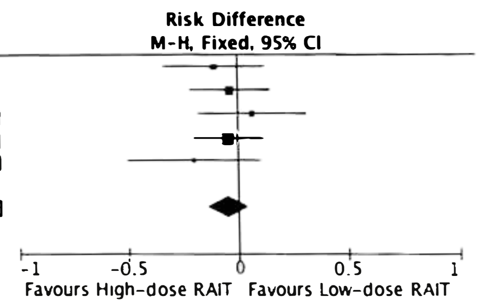

Figure 1. Weighted and pooled risk differences of the studies by Johansen et al., Bal et al., Zaman et al., Mäenpää et al., and Caglar et al. (using the strict criteria for three tests) and the resultant forest plot using a fixed effects model for the Mantel-Haenszel analysis at α = 0.05.

only the studies of Zaman et al. and Mäenpää et al. (95% confidence interval of [–0.22,0.06]) (Fig. 2).

Using a mixed effect model did not alter the above results. It is interesting to note that though the pooled risk difference has been repeatedly shown to be statistically insignificant, there exists an apparent overall trend that favours a slightly higher success rate in initial remnant ablation using high-dose RAI. This is somewhat in agreement with the result of the meta-analysis done by Doi et al. (9), albeit both observational studies and randomized clinical trials were used in that study.

In contrast to the previously published meta-analyses on the efficacy of high- and low-dose RAI therapy on patients with differentiated thyroid cancer, the authors conclude that the lack of well designed randomized controlled trials on this subject greatly hinders the conduct of a definitive meta-analysis that can be used to support the use of either high- or low-dose RAI ablation therapy. Funnel plot analysis

Study or Subgroup	Low-dose RAIT Events	Low-dose RAIT Total	High-dose RAIT Events	High-dose RAIT Total	Weight	Risk Difference M-H, Fixed, 95% CI
Maenpaa 2008	42	81	45	79	80.0%	-0.05 [-0.21, 0.10]
Zaman 2006	8	20	12	20	20.0%	-0.20 [-0.50, 0.10]
Total (95% CI)		**101**		**99**	**100.0%**	**-0.08 [-0.22, 0.06]**
Total events	50		57			
Heterogeneity: Chi² = 0.73, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 1.15 (P = 0.25)						

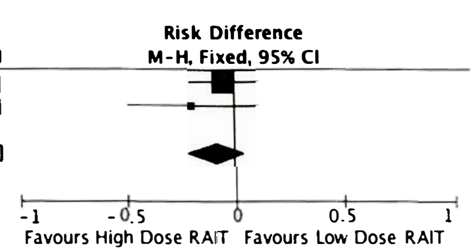

Figure 2. Weighted and pooled risk differences and resultant forest plot using a fixed effects model for the Mantel-Haenszel analysis at α = 0.05 of the results of the studies by Zaman et al. and Mäenpää et al. when a negative follow-up whole body ^{131}I scan and a serum Tg < 2 ng/mL are used to define a successful remnant ablation.

(Fig. 3) shows that there is an apparent lack of bias among the studies included in this meta-analysis but bias cannot be completely ruled out due to the low power of the included researches.

The authors recognize the difficulty in making a truly randomized controlled trial to prove the superiority of either high- or low-dose RAI ablation therapy over the other due to the nature of the pathology concerned.

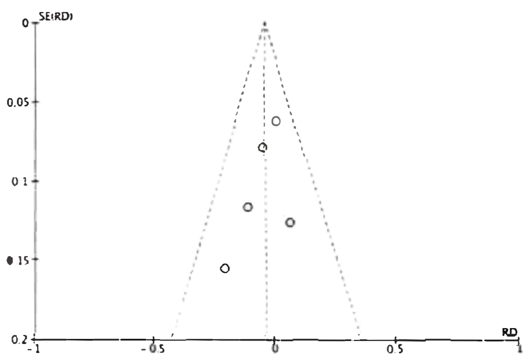

Figure 3. Funnel plot of the studies by Johansen et al., Bal et al., Zaman et al., Zaman et al., Mäenpää et al. and Caglar et al.

CONCLUSION

Though there is an apparent slightly higher success rate in using high-dose RAI ablation therapy, no definitive conclusion on its superiority over low-dose can be made at this time due to the lack of sufficient well designed randomized clinical trials. The authors therefore recommend that the choice of radioiodine activity for initial remnant ablation be still individualized based on the patient's clinical profile and experience of the clinician.

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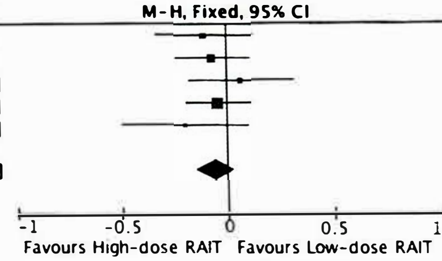
APPENDICES

Study or Subgroup	Low-dose RAIT Events	Low-dose RAIT Total	High-dose RAIT Events	High-dose RAIT Total	Weight	Risk Difference M-H, Fixed, 95% CI
Bal 1996	17	27	28	38	14.7%	-0.11 [-0.34, 0.12]
Caglar 2012	33	53	38	55	25.1%	-0.07 [-0.25, 0.11]
Johansen 1991	21	36	14	27	14.3%	0.06 [-0.18, 0.31]
Maenpaa 2008	42	81	43	77	36.7%	-0.04 [-0.20, 0.12]
Zaman 2006	8	20	12	20	9.3%	-0.20 [-0.50, 0.10]
Total (95% CI)		**217**		**217**	**100.0%**	**-0.06 [-0.15, 0.04]**
Total events	121		135			
Heterogeneity: Chi^2 = 2.03, df = 4 (P = 0.73); I^2 = 0%						
Test for overall effect: Z = 1.21 (P = 0.23)						

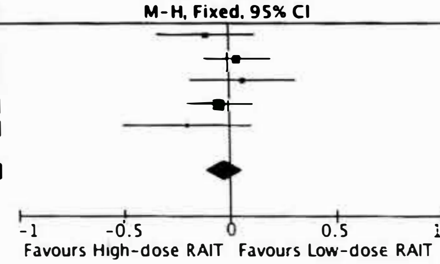
Risk Difference
M-H, Fixed, 95% CI



Appendix A1. Weighted and pooled risk differences of the studies by Johansen et al., Bal et al., Zaman et al., Mäenpää et al., and Caglar et al. (using the strict criteria for two tests) and the resultant forest plot using a fixed effects model for the Mantel-Haenszel analysis at $\alpha = 0.05$.

Study or Subgroup	Low-dose RAIT Events	Low-dose RAIT Total	High-dose RAIT Events	High-dose RAIT Total	Weight	Risk Difference M-H, Fixed, 95% CI
Bal 1996	17	27	28	38	14.7%	-0.11 [-0.34, 0.12]
Caglar 2012	43	53	42	55	25.1%	0.05 [-0.11, 0.20]
Johansen 1991	21	36	14	27	14.3%	0.06 [-0.18, 0.31]
Maenpaa 2008	42	81	43	77	36.7%	-0.04 [-0.20, 0.12]
Zaman 2006	8	20	12	20	9.3%	-0.20 [-0.50, 0.10]
Total (95% CI)		**217**		**217**	**100.0%**	**-0.03 [-0.12, 0.06]**
Total events	131		139			
Heterogeneity: Chi^2 = 3.18, df = 4 (P = 0.53); I^2 = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						

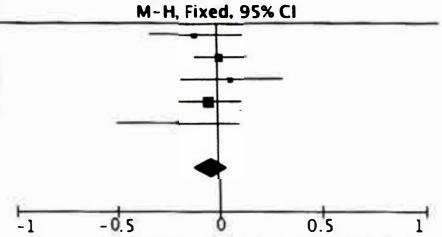
Risk Difference
M-H, Fixed, 95% CI



Appendix A2. Weighted and pooled risk differences of the studies by Johansen et al., Bal et al., Zaman et al., Mäenpää et al., and Caglar et al. (using the lax criteria for three tests) and the resultant forest plot using a fixed effects model for the Mantel-Haenszel analysis at $\alpha = 0.05$.

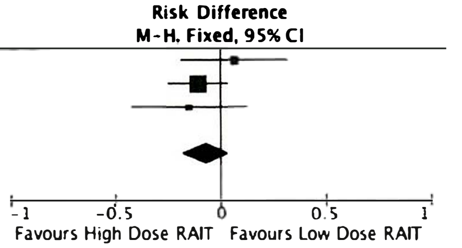
Study or Subgroup	Low-dose RAIT Events	Low-dose RAIT Total	High-dose RAIT Events	High-dose RAIT Total	Weight	Risk Difference M-H, Fixed, 95% CI
Bal 1996	17	27	28	38	14.7%	-0.11 [-0.34, 0.12]
Caglar 2012	47	53	48	55	25.1%	0.01 [-0.11, 0.14]
Johansen 1991	21	36	14	27	14.3%	0.06 [-0.18, 0.31]
Maenpaa 2008	42	81	43	77	36.7%	-0.04 [-0.20, 0.12]
Zaman 2006	8	20	12	20	9.3%	-0.20 [-0.50, 0.10]
Total (95% CI)		**217**		**217**	**100.0%**	**-0.04 [-0.12, 0.05]**
Total events	135		145			
Heterogeneity: Chi^2 = 2.77, df = 4 (P = 0.60); I^2 = 0%						
Test for overall effect: Z = 0.82 (P = 0.41)						

Risk Difference
M-H, Fixed, 95% CI



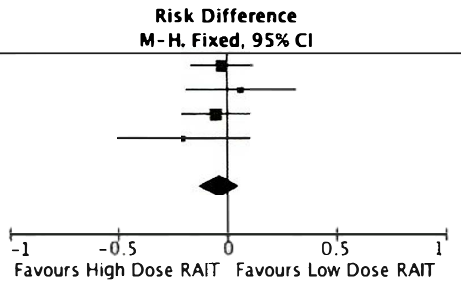
Appendix A3. Weighted and pooled risk differences of the studies by Johansen et al., Bal et al., Zaman et al., Mäenpää et al., and Caglar et al. (using the lax criteria for two tests) and the resultant forest plot using a fixed effects model for the Mantel-Haenszel analysis at $\alpha = 0.05$.

Study or Subgroup	Low-dose RAIT Events	Low-dose RAIT Total	High-dose RAIT Events	High-dose RAIT Total	Weight	Risk Difference M-H, Fixed, 95% CI
Johansen 1991	21	36	14	27	23.6%	0.06 [-0.18, 0.31]
Mäenpaa 2008	53	81	60	79	61.1%	-0.11 [-0.25, 0.03]
Zaman 2006	13	20	16	20	15.3%	-0.15 [-0.42, 0.12]
Total (95% CI)		**137**		**126**	**100.0%**	**-0.07 [-0.18, 0.04]**
Total events	87		90			
Heterogeneity: $Chi^2 = 1.70$, df = 2 (P = 0.43); $I^2 = 0\%$						
Test for overall effect: Z = 1.26 (P = 0.21)						



Appendix B1. Weighted and pooled risk differences and resultant forest plot using a fixed effects model for the Mantel-Haenszel analysis at $\alpha = 0.05$ of the results of the studies by Johansen et al., Zaman et al. and Mäenpää et al. when only a negative follow-up whole body ^{131}I scan is used to define a successful remnant ablation.

Study or Subgroup	Low-dose RAIT Events	Low-dose RAIT Total	High-dose RAIT Events	High-dose RAIT Total	Weight	Risk Difference M-H, Fixed, 95% CI
Bal 1996	59	81	51	68	36.1%	-0.02 [-0.16, 0.12]
Johansen 1991	21	36	14	27	15.1%	0.06 [-0.18, 0.31]
Mäenpäa 2008	42	81	45	79	39.1%	-0.05 [-0.21, 0.10]
Zaman 2006	8	20	12	20	9.8%	-0.20 [-0.50, 0.10]
Total (95% CI)		**218**		**194**	**100.0%**	**-0.04 [-0.13, 0.05]**
Total events	130		122			
Heterogeneity: $Chi^2 = 1.83$, df = 3 (P = 0.61); $I^2 = 0\%$						
Test for overall effect: Z = 0.80 (P = 0.43)						



Appendix B2. Weighted and pooled risk differences and resultant forest plot using a fixed effects model for the Mantel-Haenszel analysis at $\alpha = 0.05$ of the results of the studies by Bal et al., Johansen et al., Zaman et al. and Mäenpää et al. when a negative follow-up whole body ^{131}I scan and a serum Tg < 10 ng/mL are used to define a successful remnant ablation.